IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

13

In re	:	U.S. Patent No. 4,935,507
Issued	:	June 19, 1990
Patentees	:	Takao Takaya Fumiyuki Shirai Hitoshi Nakamura Yasunobu Inaba
For	:	CRYSTALLINE 7-[2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO]-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER)

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF AN APPLICATION

FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for the Product Omnicef® (cefdinir suspension), the NDA for which was approved on December 4, 1997.

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-delivered to the U.S. Patent and Trademark Office.

CAD01238.040

[X] A prescribed fee in the amount of $ 1,120.00 is required for the application presented.

Please charge Deposit Account No. 23-0455 in the amount of the prescribed fee above, or such greater or lesser amount as the Commissioner determines is required by law. This letter is submitted in triplicate for deposit account purposes.

Respectfully submitted,

January 26, 1998
Date

Charles W. Ashbrook
Registration No. 27,610
Assistant General Counsel,
Pharmaceutical Patents
WARNER-LAMBERT COMPANY
Parke-Davis Pharmaceutical
Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
Tel: (313) 996-5215
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Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156 with Declaration and attachments thereto.

[X] A certified DUPLICATE APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] Three (3) working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] This Transmittal Form in triplicate for deposit account purposes.

[X] Return Post Card.

CAD01238.040

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Number: 4,935,507

Patentees : Takao Takaya
Fumiyuki Shirai
Hitoshi Nakamura
Yasunobu Inaba

Issue Date: June 19, 1990

Title: CRYSTALLINE 7-[2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO]-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER)

APPLICATION FOR EXTENSION OF PATENT TERM

UNDER 35 U.S.C. §156

January 26, 1998
Date Mailed

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

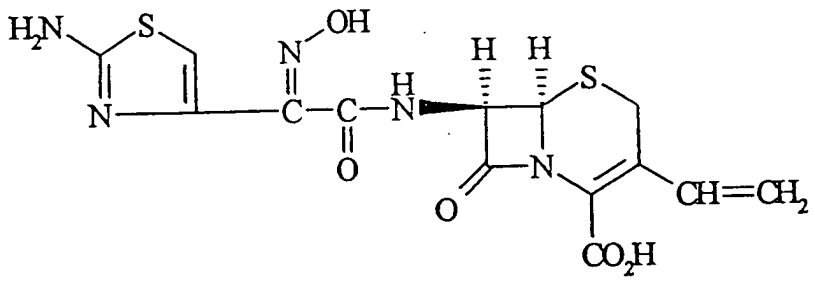
Sir:

Pursuant to §201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. §156, WARNER-LAMBERT COMPANY, of 201 Tabor Road, Morris Plains New Jersey, 07950, as agent for Fujisawa Pharmaceutical Company, Ltd., the assignee of record, hereby requests an extension of 1213 days to the 20 year term of United States Patent No. 4,935,507, thereby setting expiration to December 4, 2011. A letter from the assignee authorizing Warner-Lambert Company to submit this application is attached as Exhibit 1 (AUTHORIZATION LETTER).

The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is Omnicef® (cefdinir suspension). The active ingredient in Omnicef® is cefdinir. Omnicef® is a cephalosporin antibiotic and is approved for treatment of bacterial infections. Chemically, Omnicef® (cefdinir) is [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)-(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Another name for cefdinir is 7-[2-(2-aminothiazol-4-yl)-2-hydroxyimino-acetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer). The empirical formula of cefdinir is $C_{14}H_{13}N_5O_5S_2$; its molecular weight is 395.42; and its chemical structure is:



Cefdinir is a white to slightly brownish yellow or off-white crystalline powder that is practically insoluble in water, and slightly soluble in dilute hydrochloric acid. Omnicef® is an aqueous suspension of cefdinir for oral delivery. Cefdinir is also known within Warner-Lambert

Company as "CI-983", "FK-482" and "PD-134393", and has been assigned CAS registry No. 91832-40-5.

Omnicef® is a pharmaceutical in the form of a suspension of cefdinir for oral delivery to patients suffering from community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial otitis media, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections. Omnicef® suspension contains 125 mg of cefdinir per 5 ml of suspension. Omnicef® (cefdinir suspension) is further described in the sections titled DESCRIPTION of the PACKAGE INSERT (Exhibit 2), which is the Product Information sheet for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review of Omnicef® (cefdinir suspension) occurred under §505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §355. Section 505 provides for the submission and approval of new drug applications ("NDAs"). The original submission was under §507(b) for antibiotic drug products meeting the definition of "antibiotic drug" under 21 U.S.C. §357(a). That section was repealed by the FDA Modernization Act of 1997, and antibiotics are now "drugs" subject to review under §505.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Omnicef® (cefdinir suspension) was approved by the Food and Drug Administration ("FDA") for commercial marketing pursuant to §505(b) of the FFDCA on December 4, 1997; see Exhibit 3 (APPROVAL LETTER).

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in Omnicef® is cefdinir. Neither cefdinir, as the free acid, nor any salt or ester of cefdinir free acid, has previously been approved.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to 37 C.F.R. §1.720(f) and an identification of the date of the last day on which the application could be submitted.

The Omnicef® (cefdinir suspension) product was approved for commercial marketing on December 4, 1997, and the last day within the sixty day period permitted for submission of an application for extension of the patent is February 1, 1998. The date of submission of the present application is no later than February 1, 1998, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. PATENT NUMBER:	4,935,507
INVENTORS:	Takao Takaya Fumiyuki Shirai Hitoshi Nakamura Yasunobu Inaba
Issue Date:	June 19, 1990
Expiration Date:	August 8, 2008 (20 year term)

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent No. 4,935,507 is attached as Exhibit 4 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

No disclaimer, certificate of correction or reexamination certificate has been issued for U.S. patent No. 4,935,507. A copy of a status report showing the first and second maintenance fees, (4^{th} and 8^{th} year fees) being paid for U.S. Patent No. 4,935,507 is attached as Exhibit 5 (MAINTENANCE FEE RECEIPT).

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

U.S. Patent No. 4,935,507 claims the FDA approved product Omnicef® (cefdinir suspension) as a new chemical entity in Claim 1.

Claim 1 is set forth below:

1. Crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which shows the peaks at the diffraction angles shown in the following table in its powder X-ray diffraction pattern:

diffraction angle(°)
about 14.7
about 17.8
about 21.5
about 22.0
about 23.4
about 24.5
about 28.1

Regarding Claim 1

Claim 1 reads, in part, "Crystalline 7-[2-(2-amino-thiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)...." This is the active ingredient in Omnicef® (cefdinir suspension).

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued;

On April 30, 1990, the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company (the exclusive licensee of Fujisawa Pharmaceutical Co. Ltd.) submitted to the Food and Drug Administration an Investigational New Drug Application (IND) for cefdinir. A copy of the letter accompanying the IND submission is Exhibit 6 (IND SUBMISSION LETTER). The cover letter identified cefdinir as "CI-983 capsules". The IND was received by the FDA on May 2, 1990, and was assigned IND number 34,738, as evidenced by Exhibit 7 (IND ACKNOWLEDGMENT LETTER) attached hereto. The IND became effective on June 1, 1990 (30 days after receipt). The IND was supplemented and amended to permit clinical

studies of cefdinir powder for oral suspension, i.e. pediatric suspension (see letters dated April 11, September 19 and October 10, 1991 in Exhibit 6). Exhibits 6 and 7 establish the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1) as June 1, 1990.

On December 30, 1996, a new drug application was submitted under §507 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and §314.50 of Title 21 Code of Federal Regulations for Omnicef® (cefdinir suspension) by the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company. A copy of the cover letter attached to the NDA of December 30, 1996, is submitted herewith as Exhibit 8 (NDA SUBMISSION LETTER). The NDA was received by the FDA on December 31, 1996 and assigned number 50-749 Exhibit 9, (NDA RECEIPT LETTER).

The NDA was approved on December 4, 1997. Attached as Exhibit 3 (APPROVAL LETTER) is a copy of a letter dated December 4, 1997, from the FDA to Parke-Davis division of Warner-Lambert Company approving NDA 50-749 for the product Omnicef® (cefdinir suspension).

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. §156(g)(1), the date of the first approval of Omnicef® (cefdinir suspension) is December 4, 1997.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), the IND for Omnicef® became effective on June 1, 1990. The clinical studies under the IND are summarized in the attached Exhibit 10 (IND LOG). The IND LOG establishes that Warner-Lambert Company, through its Parke-Davis Pharmaceutical Division, worked in close consultation with the FDA, prepared detailed protocols for evaluating cefdinir, conducted extensive clinical trials, and accumulated sufficient efficacy and safety data needed to support marketing approval of Omnicef® (cefdinir suspension). These clinical studies were used to support NDA 50-749 submitted by Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company on December 30, 1996, and received by the FDA on December 31, 1996 (see Exhibit 9).

Subsequent to the submission of the NDA, WARNER-LAMBERT COMPANY had numerous contacts and meetings with the FDA with respect to the application and these are summarized in the attached Exhibit 11 (NDA LOG).

Both Exhibit 10 and Exhibit 11 have been redacted to remove confidential and non-essential information.

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension Under 35 U.S.C. §156(a)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted; (2) the term of the patent has never been extended under 35 U.S.C §156(e)(1); (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (4) the product has been subject to a regulatory review period before its commercial marketing or use; and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

As described by corresponding number, each of these elements is satisfied here:

(1) The statutory term of U.S. Patent No. 4,935,507 expires on August 8, 2008 (twenty years from filing date). The present Application has, therefore, been submitted before the expiration of the patent term. All required maintenance fees have been paid. (See Exhibit 5).

(2) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(3) This Application is submitted by Warner-Lambert Company, as authorized agent (Exhibit 1, AUTHORIZATION LETTER) for Fujisawa Pharmaceutical Co., Ltd., the owner of record of Patent 4,935,507, by assignment recorded at Reel 5234, Frames 951 - 952 (see Exhibit 12, (ASSIGNMENT RECORDATION)). This Application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date, December 4, 1997, that the Omnicef® (cefdinir suspension) product received permission for marketing under the Federal Food, Drug and

Cosmetic Act, and ending on February 1, 1998, and contains the information required under 35 U.S.C. § 156(d).

(4) As evidenced by the letter from the FDA dated December 4, 1997, Exhibit 3, (APPROVAL LETTER) the Omnicef® (cefdinir suspension) product was subject to a regulatory review period under § 505 of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of Omnicef® (cefdinir suspension) after regulatory review under §505 is the first permitted commercial marketing of cefdinir, the active ingredient in the Omnicef® (cefdinir suspension) approved product. This is confirmed by the absence of any approved new drug application under which Omnicef® (cefdinir suspension) could be commercially marketed prior to December 4, 1997.

Statement as to Length of Extension Claimed

In Accordance With 37 C.F.R. §1.775

The term of U.S. Patent No. 4,935,507 should be extended for a period of 1213 days to December 4, 2011.

The period of extension is determined in accordance with 35 U.S.C. §156 and follows the format set forth in 37 CFR §1.775(c) and (d).

37 CFR §1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. §156(g)(1)(B), it is the sum of --

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the public Health Service Act;

The number of days between the effective date of the IND, June 1, 1990, and the

initial receipt of the NDA, December 31, 1996, is a period of 2406 days

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial receipt of the NDA, December 31, 1996, to NDA approval, December 4, 1997, is a period of 339 days.

37 C.F.R. § 1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by--

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on June 1, 1990, which were on or before the date on which the patent issued, June 19, 1990, is a period of 18 days.

2406 days minus 18 days equals 2388 days;

AND

the number of days in the period of the NDA, initially submitted on December 31, 1996, which were on or before the date the patent was issued, June 19, 1990, is a period of 0 days.

339 days minus 0 days is 339 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. §156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

Applicant submits it was diligent in all matters involving Omnicef® (cefdinir suspension) and accordingly the number of days applicant did not act with due diligence is 0 days.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 2388 days equals 1194 days. (Thus, U.S. Patent No. 4,935,507 should be entitled to an extension of 1533 days (1194 IND period plus 339 NDA period)).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 1533 days to August 8, 2008, the original term of the patent (no terminal disclaimer was made), extends the term to October 19, 2012.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to December 4, 1997, the date of approval of the NDA, gives the date of December 4, 2011.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is December 4, 2011.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer;

Adding 5 years to the original expiration date of the patent (August 8, 2008) gives the date of August 8, 2013.

and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date:

Comparing December 4, 2011, and August 8, 2013, the earlier date is December 4, 2011, and the patent term should therefore be extended to December 4, 2011.

(6) If the original patent was issued before September 24, 1984,

This is not applicable for the patent.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

Applicant is unaware of any additional information material to this Application for extension.

(14) Prescribed Fee:

The prescribed fee of $1,120.00 for receiving and acting on this application for extension of patent term is hereby authorized. Please charge Deposit Account No. 23-0455 in the amount of the fee above, or such greater or lesser amount as the Commissioner determines is required by law.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Charles W. Ashbrook
Registration No. 27,610
Assistant General Counsel,
Pharmaceutical Patents
WARNER-LAMBERT COMPANY
Parke-Davis Pharmaceutical
Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
Tel: (313) 996-5215
Fax: (313) 996-1553

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith.

(17) An oath or Declaration as set forth in paragraph (b) of 37 C.F.R. §1.740.

DECLARATION

I, Charles W. Ashbrook, hereby declare that I am authorized on behalf of FUJISAWA PHARMACEUTICAL CO., LTD., the owner of record of U.S. Patent 4,935,507, to apply for an extension of the term of U.S Patent No. 4,935,507. I further declare that: I have reviewed and understand the contents of this Application being submitted pursuant to 35 U.S.C. § 156; I believe the patent is eligible for extension pursuant to 37 C.F.R. § 1.710; I believe that the length of extension claimed in this Application is fully justified under 35 U.S.C. § 156 and the applicable regulations; and I believe the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,935,507.

WARNER-LAMBERT COMPANY

Date: January 26, 1998 By: Charles W. Ashbrook

Charles W. Ashbrook
Registration No. 27,610
Assistant General Counsel,
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WARNER-LAMBERT COMPANY
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Fujisawa Pharmaceutical Co., Ltd.
Intellectual Property
1-6, Kashima 2-chome, Yodogawa-ku, Osaka 532, Japan
Telephone : 06-390-1225~9
Facsimile : 06-304-1264

Fujisawa

Exhibit 1

[Name]

[Date]

Via

Assistant Commissioner for Patents
Washington, D.C. 20231

Re : Application for Extension of United States Patent No. 4,935,507

United States Patent No. 4,935,507 is assigned to Fujisawa Pharmaceutical Company, Ltd. The assignment is recorded at Reel 5234, Frame 0951 in the United States Patent and Trademark Office.

Fujisawa Pharmaceutical Company, Ltd., as record owner of the entire right, title and interest in United States Patent No. 4,935,507, hereby appoints Warner-Lambert Company as its agent for the purpose of filing an application for extension of the term of United States Patent No. 4,935,507 under 35 U.S.C. § 156, and hereby grants a Power of Attorney to the following individuals for purposes of filing and prosecuting the application for extension:

Charles W. Ashbrook	Registration No. 27,610
Todd M. Crissey	Registration No. 37,807
Francis J. Tinney	Registration No. 33,069

Fujisawa Pharmaceutical Company, Ltd.

By: Yoshikazu Nishide

Name: Yoshikazu Nishide

Title: Director, Intellectual Property

EXHIBIT 1

AUTHORIZATION LETTER

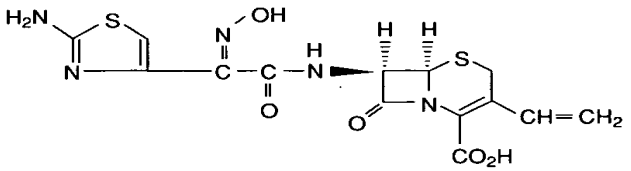
EXHIBIT 2

PACKAGE INSERT

Omnicef® (Cefdinir) Capsules
Omnicef® (Cefdinir) for Oral Suspension

DESCRIPTION

OMNICEF® (cefdinir) Capsules and OMNICEF® (cefdinir) for Oral Suspension contain the active ingredient cefdinir, an extended-spectrum, semisynthetic cehalosporin, for oral administration. Chemically, cefdinir is [6R-[6α,7β (Z)]]-7-[[(2-amino-4-thiazolyl)-(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Cefdinir is a white to slightly brownish-yellow solid. It is slightly soluble in dilute hydrochloric acid and sparingly soluble in 0.1 M pH 7.0 phosphate buffer. The empirical formula is $C_{14}H_{13}N_5O_5S_2$ and the molecular weight is 395.42. Cefdinir has the structural formula shown below:



OMNICEF Capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, NF; polyoxyl 40 stearate, NF; magnesium stearate, NF; and silicon dioxide, NF. The capsule shells contain FD&C Blue #1; FD&C Red #40; D&C Red #28; titanium dioxide, NF; gelatin, NF; and sodium lauryl sulfate, NF.

OMNICEF for Oral Suspension, after reconstitution, contains 125 mg cefdinir per 5 mL and the following inactive ingredients: sucrose, NF; citric acid, USP; sodium citrate, USP; sodium benzoate, NF; xanthan gum, NF; guar gum, NF; artificial strawberry and cream flavors; silicon dioxide, NF; and magnesium stearate, NF.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Drug Metabolism

Absorption:

Oral Bioavailability: Maximal plasma cefdinir concentrations occur 2 to 4 hours postdose following capsule or suspension administration. Plasma cefdinir concentrations increase with dose, but the increases are less than dose-proportional from 300 mg (7 mg/kg) to 600 mg (14 mg/kg). Following administration of suspension to healthy adults, cefdinir bioavailability is 120% relative to capsules. Estimated bioavailability of cefdinir capsules is 21% following administration of a 300 mg capsule dose, and 16% following administration of a 600 mg capsule dose. Estimated absolute bioavailability of cefdinir suspension is 25%.

Effect of Food: Although the rate (C_{max}) and extent (AUC) of cefdinir absorption from the capsules are reduced by 16% and 10%, respectively, when given with a high-fat meal, the magnitude of these reductions is not likely to be clinically significant. Therefore, cefdinir may be taken without regard to food.

Cefdinir Capsules: Cefdinir plasma concentrations and pharmacokinetic parameter values following administration of single 300- and 600-mg oral doses of cefdinir to adult subjects are presented in the following table:

Mean (±SD) Plasma Cefdinir Pharmacokinetic Parameter Values Following Administration of Capsules to Adult Subjects

Dose	C_{max} (μg/mL)	t_{max} (hr)	AUC (μg·hr/mL)
300 mg	1.60	2.9	7.05
	(0.55)	(0.89)	(2.17)
600 mg	2.87	3.0	11.1
	(1.01)	(0.66)	(3.87)

Cefdinir Suspension: Cefdinir plasma concentrations and pharmacokinetic parameter values following administration of single 7- and 14-mg/kg oral doses of cefdinir to pediatric subjects (age 6 months–12 years) are presented in the following table:

Mean (±SD) Plasma Cefdinir Pharmacokinetic Parameter Values Following Administration of Suspension to Pediatric Subjects

Dose	C_{max} (μg/mL)	t_{max} (hr)	AUC (μg·hr/mL)
7 mg/kg	2.30	2.2	8.31
	(0.65)	(0.6)	(2.50)
14 mg/kg	3.86	1.8	13.4
	(0.62)	(0.4)	(2.64)

Multiple Dosing: Cefdinir does not accumulate in plasma following once- or twice-daily administration to subjects with normal renal function.

Distribution: The mean volume of distribution (Vd_{area}) of cefdinir in adult subjects is 0.35 L/kg (±0.29); in pediatric subjects (age 6 months–12 years), cefdinir Vd_{area} is 0.67 L/kg (±0.38). Cefdinir is 60% to 70% bound to plasma proteins in both adult and pediatric subjects; binding is independent of concentration.

Skin Blister: In adult subjects, median (range) maximal blister fluid cefdinir concentrations

Omnicef® (Cefdinir) Capsules
Omnicef® (Cefdinir) for Oral Suspension

For organisms other than *Haemophilus* spp. and *Streptococcus* spp:

MIC (μg/mL)	Interpretation
≤1	Susceptible (S)
2	Intermediate (I)
≥4	Resistant (R)

For *Haemophilus* spp:[a]

MIC (μg/mL)	Interpretation[b]
≤1	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM).[1]

[b] The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus* spp:

Streptococcus pneumoniae that are susceptible to penicillin (MIC ≤0.06 μg/mL), or streptococci other than *S. pneumoniae* that are susceptible to penicillin (MIC ≤0.12 μg/mL), can be considered susceptible to cefdinir. Testing of cefdinir against penicillin-intermediate or penicillin-resistant isolates is not recommended. Reliable interpretive criteria for cefdinir are not available.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures. Standard cefdinir powder should provide the following MIC values:

Microorganism	MIC Range (μg/mL)
Escherichia coli ATCC 25922	0.12-0.5
Haemophilus influenzae ATCC 49766[c]	0.12-0.5
Staphylococcus aureus ATCC 29213	0.12-0.5

[c] This quality control range is applicable only to *H. influenzae* ATCC 49766 tested by a broth microdilution procedure using HTM.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-μg cefdinir to test the susceptibility of microorganisms to cefdinir.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-μg cefdinir disk should be interpreted according to the following criteria:

For organisms other than *Haemophilus* spp. and *Streptococcus* spp:[d]

Zone Diameter (mm)	Interpretation
≥20	Susceptible (S)
17-19	Intermediate (I)
≤16	Resistant (R)

[d] Because certain strains of *Citrobacter, Providencia,* and *Enterobacter* spp. have been reported to give false susceptible results with the cefdinir disk, strains of these genera should not be tested and reported with this disk.

For *Haemophilus* spp:[e]

Zone Diameter (mm)	Interpretation[f]
≥20	Susceptible

[e] These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM.[2]

[f] The current absence of data on resistant strains precludes defining any results other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus* spp:

Isolates of *Streptococcus pneumoniae* should be tested against a 1-μg oxacillin disk. Isolates with oxacillin zone sizes ≥20 mm are susceptible to penicillin and can be considered susceptible to cefdinir. Streptococci other than *S. pneumoniae* should be tested with a 10-unit penicillin disk. Isolates with penicillin zone sizes ≥28 mm are susceptible to penicillin and can be considered susceptible to cefdinir.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for cefdinir.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of laboratory procedures. For the diffusion technique, the 5-μg cefdinir disk should provide the following zone diameters in these laboratory quality control strains:

plasma levels, and a 50% prolongation in the apparent elimination half-life.

Iron Supplements and Foods Fortified With Iron: Concomitant administration of cefdinir with a therapeutic iron supplement containing 60 mg of elemental iron (as $FeSO_4$) or vitamins supplemented with 10 mg of elemental iron reduced extent of absorption by 80% and 31%, respectively. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement.

The effect of foods highly fortified with elemental iron (primarily iron-fortified breakfast cereals) on cefdinir absorption has not been studied.

Concomitantly administered iron-fortified infant formula (2.2 mg elemental iron/6 oz) has no significant effect on cefdinir pharmacokinetics. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

There have been rare reports of reddish stools in patients who have received cefdinir in Japan. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products and iron in the gastrointestinal tract.

Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferricyanide. The administration of cefdinir may result in a false-positive reaction for glucose in urine using Clinitest®, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® or Tes-Tape®) be used. Cephalosporins are known to occasionally induce a positive direct Coombs' test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of cefdinir has not been evaluated. No mutagenic effects were seen in the bacterial reverse mutation assay (Ames) or point mutation assay at the hypoxanthine-guanine phosphoribosyltransferase locus (HGPRT) in V79 Chinese hamster lung cells. No clastogenic effects were observed *in vitro* in the structural chromosome aberration assay in V79 Chinese hamster lung cells or *in vivo* in the micronucleus assay in mouse bone marrow. In rats, fertility and reproductive performance were not affected by cefdinir at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m^2/day).

Pregnancy - Teratogenic Effects

Pregnancy Category B: Cefdinir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m^2/day) or in rabbits at oral doses up to 10 mg/kg/day (0.7 times the human dose based on mg/kg/day, 0.23 times based on mg/m^2/day). Maternal toxicity (decreased body weight gain) was observed in rabbits at the maximum tolerated dose of 10 mg/kg/day without adverse effects on offspring. Decreased body weight occurred in rat fetuses at ≥100 mg/kg/day, and in rat offspring at ≥32 mg/kg/day. No effects were observed on maternal reproductive parameters or offspring survival, development, behavior, or reproductive function.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Cefdinir has not been studied for use during labor and delivery.

Nursing Mothers

Following administration of single 600-mg doses, cefdinir was not detected in human breast milk.

Pediatric Use

Safety and efficacy in neonates and infants less than 6 months of age have not been established. Use of cefdinir for the treatment of acute maxillary sinusitis in pediatric patients (age 6 months through 12 years) is supported by evidence from adequate and well-controlled studies in adults and adolescents, the similar pathophysiology of acute sinusitis in adult and pediatric patients, and comparative pharmacokinetic data in the pediatric population.

Geriatric Use

Efficacy is comparable in geriatric patients and younger adults. While cefdinir has been well-tolerated in all age groups, in clinical trials geriatric patients experienced a lower rate of adverse events, including diarrhea, than younger adults. Dose adjustment in elderly patients is not necessary unless renal function is markedly compromised (see **DOSAGE AND ADMINISTRATION**).

ADVERSE EVENTS

Clinical Trials - OMNICEF Capsules (Adult and Adolescent Patients):

In clinical trials, 4527 adult and adolescent patients (3275 US and 1252 non-US) were treated with the recommended dose of cefdinir capsules (600 mg/day). Most adverse events were mild and self-limiting in nature. No deaths or permanent disabilities were attributed to cefdinir. One hundred twenty-five of 4527 (3%) patients discontinued medication due to adverse events thought by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. The discontinuations were primarily for gastrointestinal disturbances, usually diarrhea or nausea. Seventeen of 4527 (0.4%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by the investigators to be possibly, probably, or definitely related to cefdinir capsules in multiple-dose clinical trials (N = 3275 cefdinir-treated patients):

ADVERSE EVENTS ASSOCIATED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N=3275)[a]

Incidence ≥1%	Diarrhea	16%
	Vaginal moniliasis	5% of women
	Nausea	3%
	Headache	2%
	Abdominal pain	1%
	Vaginitis	1% of women
Incidence <1% but >0.1%	Rash	0.9%
	Dyspepsia	0.8%
	Flatulence	0.6%
	Vomiting	0.6%
	Anorexia	0.3%
	Constipation	0.3%
	Abnormal stools	0.2%
	Asthenia	0.2%
	Dizziness	0.2%
	Insomnia	0.2%
	Leukorrhea	0.2% of women
	Pruritus	0.2%
	Somnolence	0.2%

[a] 1469 males, 1806 females

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

LABORATORY VALUE CHANGES OBSERVED WITH CEFDINIR CAPSULES US TRIALS IN ADULT AND ADOLESCENT PATIENTS (N = 3275)

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dosage, particularly if renal function is compromised.

DOSAGE AND ADMINISTRATION
(see **INDICATIONS AND USAGE** for Indicated Pathogens)

Capsules

The recommended dosage and duration of treatment for infections in adults and adolescents are described in the following chart; the total daily dose for all infections is 600 mg. Once-daily dosing for 10 days is as effective as BID dosing. Once-daily dosing has not been studied in pneumonia or skin infections; therefore, OMNICEF Capsules should be administered twice daily in these infections. OMNICEF Capsules may be taken without regard to meals.

Adults and Adolescents (Age 13 Years and Older)

Type of Infection	Dosage	Duration
Community-Acquired Pneumonia	300 mg q12h	10 days
Acute Exacerbations of Chronic Bronchitis	300 mg q12h	10 days
	or	
	600 mg q24h	10 days
Acute Maxillary Sinusitis	300 mg q12h	10 days
	or	
	600 mg q24h	10 days
Pharyngitis/Tonsillitis	300 mg q12h	5 to 10 days
	or	
	600 mg q24h	10 days
Uncomplicated Skin and Skin Structure Infections	300 mg q12h	10 days

Powder for Oral Suspension

The recommended dosage and duration of treatment for infections in pediatric patients are described in the following chart; the total daily dose for all infections is 14 mg/kg, up to a maximum dose of 600 mg per day. Once-daily dosing for 10 days is as effective as BID dosing. Once-daily dosing has not been studied in skin infections; therefore, OMNICEF for Oral Suspension should be administered twice daily in this infection. OMNICEF for Oral Suspension may be administered without regard to meals.

Pediatric Patients (Age 6 Months Through 12 Years)

Type of Infection	Dosage	Duration
Acute Bacterial Otitis Media	7 mg/kg q12h	10 days
	or	
	14 mg/kg q24h	10 days
Acute Maxillary Sinusitis	7 mg/kg q12h	10 days
	or	
	14 mg/kg q24h	10 days
Pharyngitis/Tonsillitis	7 mg/kg q12h	5 to 10 days
	or	
	14 mg/kg q24h	10 days
Uncomplicated Skin and Skin Structure Infections	7 mg/kg q12h	10 days

OMNICEF FOR ORAL SUSPENSION PEDIATRIC DOSAGE CHART

Weight	125 mg/5 mL
9 kg/20 lbs	2.5 mL (½ tsp) q12h or 5 mL (1 tsp) q24h
18 kg/40 lbs	5 mL (1 tsp) q12h or 10 mL (2 tsp) q24h
27 kg/60 lbs	7.5 mL (1½ tsp) q12h or 15 mL (3 tsp) q24h
36 kg/80 lbs	10 mL (2 tsp) q12h or 20 mL (4 tsp) q24h
≥ 43 kg[a]/95 lbs	12 mL (2½ tsp) q12h or 24 mL (5 tsp) q24h

[a] Pediatric patients who weigh ≥43 kg should receive the maximum daily dose of 600 mg.

Patients With Renal Insufficiency

For adult patients with creatinine clearance <30 mL/min, the dose of cefdinir should be 300 mg given once daily.

Creatinine clearance is difficult to measure in outpatients. However, the following formula may be used to estimate creatinine clearance (CL_{cr}) in adult patients. For estimates to be valid, serum creatinine levels should reflect steady-state levels of renal function.

Males: $$CL_{cr} = \frac{(\text{weight})\ (140 - \text{age})}{(72)\ (\text{serum creatinine})}$$

Females: $CL_{cr} = 0.85 \times$ above value

where creatinine clearance is in mL/min, age is in years, weight is in kilograms, and serum creatinine is in mg/dL.[3]

The following formula may be used to estimate creatinine clearance in pediatric patients:

$$CL_{cr} = K \times \frac{\text{body length or height}}{\text{serum creatinine}}$$

where K=0.55 for pediatric patients older than 1 year[4] and 0.45 for infants (up to 1 year)[5].

In the above equation, creatinine clearance is in mL/min/1.73 m^2, body length or height is in centimeters, and serum creatinine is in mg/dL.

For pediatric patients with a creatinine clearance of <30 mL/min/1.73 m^2, the dose of cefdinir should be 7 mg/kg (up to 300 mg) given once daily.

Patients on Hemodialysis

Hemodialysis removes cefdinir from the body. In patients maintained on chronic hemodialysis, the recommended initial dosage regimen is a 300-mg or 7-mg/kg dose every other day. At the conclusion of each hemodialysis session, 300 mg (or 7 mg/kg) should be given. Subsequent doses (300 mg or 7 mg/kg) are then administered every other day.

Directions for Mixing OMNICEF for Oral Suspension

Final Concentration	Final Volume (mL)	Amount of Water	Directions
125 mg/5 mL	60	39 mL	Tap bottle to loosen powder, then add water in 2 portions. Shake well after each aliquot.
	100	65 mL	

After mixing, the suspension can be stored at room temperature (25°C/77°F). The container should be kept tightly closed, and the suspension should be shaken well before each administration. The suspension may be used for 10 days, after which any unused portion must be discarded.

HOW SUPPLIED

OMNICEF Capsules, containing 300 mg cefdinir, as lavender and turquoise capsules imprinted with the product name, are available as follows:

60 Capsules/Bottle N 0071-0067-20

[redacted] colored powder formulation that, when recon-

	↑Urine red blood cells	1%
Incidence <1% but >0.1%	↑Glucose, ↓ Glucose	0.9, 0.2
	↑Alanine aminotransferase (ALT)	0.9
	↑Urine glucose	0.9
	↑White blood cells, ↓White blood cells	0.8, 0.7
	↓Lymphocytes, ↑Lymphocytes	0.8, 0.2
	↑Urine specific gravity	0.8
	↓Bicarbonate	0.6
	↑Eosinophils	0.6
	↑Phosphorus, ↓Phosphorus	0.6, 0.3
	↑Aspartate aminotransferase (AST)	0.4
	↑Urine white blood cells	0.4
	↓Hemoglobin	0.3
	↑Alkaline phosphatase	0.2
	↑Blood urea nitrogen (BUN)	0.2
	↑Bilirubin	0.2
	↑Lactate dehydrogenase	0.2
	↑Platelets	0.2
	↓Polymorphonuclear neutrophils (PMNs)	0.2
	↑Potassium	0.2
	↑Urine pH	0.2

Clinical Trials - OMNICEF for Oral Suspension (Pediatric Patients):

In clinical trials, 1893 pediatric patients (1387 US and 506 non-US) were treated with the recommended dose of cefdinir suspension (14 mg/kg/day). Most adverse events were mild and self-limiting. No deaths or permanent disabilities were attributed to cefdinir. Thirty-nine of 1893 (2%) patients discontinued medication due to adverse events considered by the investigators to be possibly, probably, or definitely associated with cefdinir therapy. Discontinuations were primarily for gastrointestinal disturbances, usually diarrhea. Five of 1893 (0.3%) patients were discontinued due to rash thought related to cefdinir administration.

In the US, the following adverse events were thought by investigators to be possibly, probably, or definitely related to cefdinir suspension in multiple-dose clinical trials (N=1387 cefdinir-treated patients):

ADVERSE EVENTS ASSOCIATED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N = 1387)[a]

Incidence ≥ 1%	Diarrhea	8%
	Rash	3%
	Cutaneous moniliasis	1%
	Vomiting	1%
Incidence <1% but >0.1%	Abdominal pain	0.9%
	Leukopenia[b]	0.4%
	Nausea	0.3%
	Vaginal moniliasis	0.3% of girls
	Vaginitis	0.3% of girls
	Dyspepsia	0.2%
	Maculopapular rash	0.2%
	Increased AST[b]	0.2%

[a] 743 males, 644 females
[b] Laboratory changes were occasionally reported as adverse events.

The following laboratory value changes of possible clinical significance, irrespective of relationship to therapy with cefdinir, were seen during clinical trials conducted in the US:

LABORATORY VALUE CHANGES OBSERVED WITH CEFDINIR SUSPENSION US TRIALS IN PEDIATRIC PATIENTS (N = 1387)

Incidence ≥1%	↑Lactate dehydrogenase	2%
	↑Alkaline phosphatase	1%
	↓Bicarbonate	1%
	↑Eosinophils	1%
	↑Urine pH	1%
Incidence <1% but >0.1%	↑Lymphocytes, ↓Lymphocytes	0.9, 0.7
	↑Phosphorus, ↓Phosphorus	0.9, 0.4
	↓White blood cells, ↑White blood cells	0.9, 0.4
	↑Urine protein	0.9
	↑PMNs	0.8
	↑Platelets	0.7
	↓Calcium	0.5
	↑AST	0.2
	↓Hemoglobin	0.4
	↑Potassium	0.3
	↑ALT	0.2
	↓Hematocrit	0.2
	↑Urine specific gravity	0.2
	↑Urine white blood cells	0.2

Postmarketing Experience

The following adverse experiences and altered laboratory tests, regardless of their relationship to cefdinir, have been reported during extensive postmarketing experience, beginning with approval in Japan in 1991: Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, erythema nodosum, conjunctivitis, stomatitis, acute hepatitis, cholestasis, fulminant hepatitis, hepatic failure, jaundice, increased amylase, shock, anaphylaxis, facial and laryngeal edema, feeling of suffocation, acute enterocolitis, bloody diarrhea, hemorrhagic colitis, melena, pseudomembranous colitis, pancytopenia, granulocytopenia, leukopenia, thrombocytopenia, idiopathic thrombocytopenic purpura, hemolytic anemia, acute respiratory failure, asthmatic attack, drug-induced pneumonia, eosinophilic pneumonia, idiopathic interstitial pneumonia, fever, acute renal failure, nephropathy, bleeding tendency, coagulation disorder, disseminated intravascular coagulation, upper GI bleed, peptic ulcer, ileus, loss of consciousness, allergic vasculitis, possible cefdinir-diclofenac interaction, cardiac failure, chest pain, myocardial infarction, hypertension, involuntary movements, and rhabdomyolysis.

Cephalosporin Class Adverse Events

The following adverse events and altered laboratory tests have been reported for cephalosporin-class antibiotics in general:

Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive test for urinary glucose, neutropenia, pancytopenia, and agranulocytosis. Pseudomembranous colitis symptoms may begin during or after antibiotic treatment (see **WARNINGS**).

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

Information on cefdinir overdosage in humans is not available. In acute rodent toxicity studies, a single oral 5600-mg/kg dose produced no adverse effects. Toxic signs and symptoms following overdosage with other β-lactam antibiotics have included nausea, vomiting, epigastric distress, diarrhea, and convulsions. Hemodialysis removes cefdinir from the body. This may be useful in the event of a serious toxic reaction from overdosage.

cream color and strawberry flavor. The powder is available as follows:

60-mL bottles	N 0071-2006-16
100-mL bottles	N 0071-2006-18

Store the capsules and unsuspended powder at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Once reconstituted, the oral suspension can be stored at controlled room temperature for 10 days.

CLINICAL STUDIES

Community-Acquired Bacterial Pneumonia

In a controlled, double-blind study in adults and adolescents conducted in the US, cefdinir BID was compared with cefaclor 500 mg TID. Using strict evaluability and microbiologic/clinical response criteria 6 to 14 days posttherapy, the following clinical cure rates, presumptive microbiologic eradication rates, and statistical outcomes were obtained (see table below):

US Community-Acquired Pneumonia Study
Cefdinir vs Cefaclor

	Cefdinir BID	Cefaclor TID	Outcome
Clinical Cure Rates	150/187 (80%)	147/186 (79%)	Cefdinir equivalent to control
Eradication Rates			
Overall	177/195 (91%)	184/200 (92%)	Cefdinir equivalent to control
S. pneumoniae	31/31 (100%)	35/35 (100%)	
H. influenzae	55/65 (85%)	60/72 (83%)	
M. catarrhalis	10/10 (100%)	11/11 (100%)	
H. parainfluenzae	81/89 (91%)	78/82 (95%)	

In a second controlled, investigator-blind study in adults and adolescents conducted primarily in Europe, cefdinir BID was compared with amoxicillin/clavulanate 500/125 mg TID. Using strict evaluability and clinical response criteria 6 to 14 days posttherapy, the following clinical cure rates, presumptive microbiologic eradication rates, and statistical outcomes were obtained (see table below):

European Community-Acquired Pneumonia Study
Cefdinir vs Amoxicillin/Clavulanate

	Cefdinir BID	Amoxicillin/ Clavulanate TID	Outcome
Clinical Cure Rates	83/104 (80%)	86/97 (89%)	Cefdinir not equivalent to control
Eradication Rates			
Overall	85/96 (89%)	84/90 (93%)	Cefdinir equivalent to control
S. pneumoniae	42/44 (95%)	43/44 (98%)	
H. influenzae	26/35 (74%)	21/26 (81%)	
M. catarrhalis	6/6 (100%)	8/8 (100%)	
H. parainfluenzae	11/11 (100%)	12/12 (100%)	

Streptococcal Pharyngitis/Tonsillitis

In four controlled studies conducted in the United States, cefdinir was compared with 10 days of penicillin in adults, adolescents, and pediatric patients. Two studies (one in adults and adolescents, the other in pediatric patients) compared 10 days of cefdinir QD or BID to penicillin 250 mg or 10 mg/kg QID. Using strict evaluability and microbiologic/clinical response criteria 5 to 10 days posttherapy, the following clinical cure rates, microbiologic eradication rates, and statistical outcomes were obtained (see table below):

Pharyngitis/Tonsillitis Studies
Cefdinir (10 days) vs Penicillin (10 days)

Study	Efficacy Parameter	Cefdinir QD	Cefdinir BID	Penicillin QID	Outcome
Adults/ Adolescents	Eradication of *S. pyogenes*	192/210 (91%)	199/217 (92%)	181/217 (83%)	Cefdinir superior to control
	Clinical Cure Rates	199/210 (95%)	209/217 (96%)	193/217 (89%)	Cefdinir superior to control
Pediatric Patients	Eradication of *S. pyogenes*	215/228 (94%)	214/227 (94%)	159/227 (70%)	Cefdinir superior to control
	Clinical Cure Rates	222/228 (97%)	218/227 (96%)	196/227 (86%)	Cefdinir superior to control

Two studies (one in adults and adolescents, the other in pediatric patients) compared 5 days of cefdinir BID to 10 days of penicillin 250 mg or 10 mg/kg QID. Using strict evaluability and microbiologic/clinical response criteria 4 to 10 days posttherapy, the following clinical cure rates, microbiologic eradication rates, and statistical outcomes were obtained (see table below):

Pharyngitis/Tonsillitis Studies
Cefdinir (5 days) vs Penicillin (10 days)

Study	Efficacy Parameter	Cefdinir BID	Penicillin QID	Outcome
Adults/ Adolescents	Eradication of *S. pyogenes*	193/218 (89%)	176/214 (82%)	Cefdinir equivalent to control
	Clinical Cure Rates	194/218 (89%)	181/214 (85%)	Cefdinir equivalent to control
Pediatric Patients	Eradication of *S. pyogenes*	176/196 (90%)	135/193 (70%)	Cefdinir superior to control
	Clinical Cure Rates	179/196 (91%)	173/193 (90%)	Cefdinir equivalent to control

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Caution: Federal law prohibits dispensing without prescription.

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Manufactured by:
Lilly del Caribe, Inc.
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For:
PARKE-DAVIS
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Morris Plains, NJ 07950 USA

0067G050

istration of 300- and 600-mg doses, respectively. Mean (±SD) blister C_{max} and AUC (0-∞) values were 48% (±13) and 91% (±18) of corresponding plasma values.

Tonsil Tissue: In adult patients undergoing elective tonsillectomy, respective median tonsil tissue cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.25 (0.22-0.46) and 0.36 (0.22-0.80) µg/g. Mean tonsil tissue concentrations were 24% (±8) of corresponding plasma concentrations.

Sinus Tissue: In adult patients undergoing elective maxillary and ethmoid sinus surgery, respective median sinus tissue cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were <0.12 (<0.12-0.46) and 0.21 (<0.12-2.0) µg/g. Mean sinus tissue concentrations were 16% (±20) of corresponding plasma concentrations.

Lung Tissue: In adult patients undergoing diagnostic bronchoscopy, respective median bronchial mucosa cefdinir concentrations 4 hours after administration of single 300- and 600-mg doses were 0.78 (<0.06-1.33) and 1.14 (<0.06-1.92) µg/mL, and were 31% (±18) of corresponding plasma concentrations. Respective median epithelial lining fluid concentrations were 0.29 (<0.3-4.73) and 0.49 (<0.3-0.59) µg/mL, and were 35% (±83) of corresponding plasma concentrations.

Middle Ear Fluid: In 14 pediatric patients with acute bacterial otitis media, respective median middle ear fluid cefdinir concentrations 3 hours after administration of single 7- and 14-mg/kg doses were 0.21 (<0.09-0.94) and 0.72 (0.14-1.42) µg/mL. Mean middle ear fluid concentrations were 15% (±15) of corresponding plasma concentrations.

CSF: Data on cefdinir penetration into human cerebrospinal fluid are not available.

Metabolism and Excretion: Cefdinir is not appreciably metabolized. Activity is primarily due to parent drug. Cefdinir is eliminated principally via renal excretion with a mean plasma elimination half-life ($t_{1/2}$) of 1.7 (±0.6) hours. In healthy subjects with normal renal function, renal clearance is 2.0 (±1.0) mL/min/kg, and apparent oral clearance is 11.6 (±6.0) and 15.5 (±5.4) mL/min/kg following doses of 300- and 600-mg, respectively. Mean percent of dose recovered unchanged in the urine following 300- and 600-mg doses is 18.4% (±6.4) and 11.6% (±4.6), respectively. Cefdinir clearance is reduced in patients with renal dysfunction (see **Special Populations:** *Patients with Renal Insufficiency*).

Because renal excretion is the predominant pathway of elimination, dosage should be adjusted in patients with markedly compromised renal function or who are undergoing hemodialysis (see **DOSAGE AND ADMINISTRATION**).

Special Populations:

Patients with Renal Insufficiency: Cefdinir pharmacokinetics were investigated in 21 adult subjects with varying degrees of renal function. Decreases in cefdinir elimination rate, apparent oral clearance (CL/F), and renal clearance were approximately proportional to the reduction in creatinine clearance (CL_{cr}). As a result, plasma cefdinir concentrations were higher and persisted longer in subjects with renal impairment than in those without renal impairment. In subjects with CL_{cr} between 30 and 60 mL/min, C_{max} and $t_{1/2}$ increased by approximately 2-fold and AUC by approximately 3-fold. In subjects with CL_{cr} <30 mL/min, C_{max} increased by approximately 2-fold, $t_{1/2}$ by approximately 5-fold, and AUC by approximately 6-fold. Dosage adjustment is recommended in patients with markedly compromised renal function (creatinine clearance <30 mL/min; see **DOSAGE AND ADMINISTRATION**).

Hemodialysis: Cefdinir pharmacokinetics were studied in 8 adult subjects undergoing hemodialysis. Dialysis (4 hours duration) removed 63% of cefdinir from the body and reduced apparent elimination $t_{1/2}$ from 16 (±3.5) to 3.2 (±1.2) hours. Dosage adjustment is recommended in this patient population (see **DOSAGE AND ADMINISTRATION**).

Hepatic Disease: Because cefdinir is predominantly renally eliminated and not appreciably metabolized, studies in patients with hepatic impairment were not conducted. It is not expected that dosage adjustment will be required in this population.

Geriatric Patients: The effect of age on cefdinir pharmacokinetics after a single 300-mg dose was evaluated in 32 subjects 19 to 91 years of age. Systemic exposure to cefdinir was substantially increased in older subjects (N=16), C_{max} by 44% and AUC by 86%. This increase was due to a reduction in cefdinir clearance. The apparent volume of distribution was also reduced, thus no appreciable alterations in apparent elimination half-life were observed (elderly: 2.2 ± 0.6 hours vs young: 1.8 ± 0.4 hours). Since cefdinir clearance has been shown to be primarily related to changes in renal function rather than age, elderly patients do not require dosage adjustment unless they have markedly compromised renal function (creatinine clearance <30 mL/min, see *Patients with Renal Insufficiency*, above).

Gender and Race: The results of a meta-analysis of clinical pharmacokinetics (N=217) indicated no significant impact of either gender or race on cefdinir pharmacokinetics.

Microbiology

As with other cephalosporins, bactericidal activity of cefdinir results from inhibition of cell wall synthesis. Cefdinir is stable in the presence of some, but not all, β-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins are susceptible to cefdinir.

Cefdinir has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE**.

Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (including β-lactamase producing strains)
NOTE: Cefdinir is inactive against methicillin-resistant staphylococci.
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic Gram-Negative Microorganisms:

Haemophilus influenzae (including β-lactamase producing strains)
Haemophilus parainfluenzae (including β-lactamase producing strains)
Moraxella catarrhalis (including β-lactamase producing strains)

The following *in vitro* data are available, **but their clinical significance is unknown.**

Cefdinir exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against (≥90%) strains of the following microorganisms; however, the safety and effectiveness of cefdinir in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Microorganisms:

Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus agalactiae
Viridans group streptococci

NOTE: Cefdinir is inactive against *Enterococcus* and methicillin-resistant *Staphylococcus* species.

Aerobic Gram-Negative Microorganisms:

Citrobacter diversus
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

NOTE: Cefdinir is inactive against *Pseudomonas* and *Enterobacter* species.

Susceptibility Tests:

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of cefdinir powder. The MIC values should be interpreted according to the following criteria:

Organism	Zone Diameter (mm)
Escherichia coli ATCC 25922	24-28
Haemophilus influenzae ATCC 49766[9]	24-31
Staphylococcus aureus ATCC 25923	25-32

9 This quality control range is applicable only to testing of *H. influenzae* ATCC 49766 using HTM.

INDICATIONS AND USAGE

OMNICEF (cefdinir) Capsules and OMNICEF (cefdinir) for Oral Suspension are indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Adults and Adolescents

Community-Acquired Pneumonia caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains) (see **CLINICAL STUDIES**).

Acute Exacerbations of Chronic Bronchitis caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Haemophilus parainfluenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

Acute Maxillary Sinusitis caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

NOTE: For information on use in pediatric patients, See **Pediatric Use** and **DOSAGE AND ADMINISTRATION**.

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes* (see **CLINICAL STUDIES**).

NOTE: Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*.

Pediatric Patients

Acute Bacterial Otitis Media caused by *Haemophilus influenzae* (including β-lactamase producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including β-lactamase producing strains).

Pharyngitis/Tonsillitis caused by *Streptococcus pyogenes* (see **CLINICAL STUDIES**).

NOTE: Cefdinir is effective in the eradication of *S. pyogenes* from the oropharynx. Cefdinir has not, however, been studied for the prevention of rheumatic fever following *S. pyogenes* pharyngitis/tonsillitis. Only intramuscular penicillin has been demonstrated to be effective for the prevention of rheumatic fever.

Uncomplicated Skin and Skin Structure Infections caused by *Staphylococcus aureus* (including β-lactamase producing strains) and *Streptococcus pyogenes*.

CONTRAINDICATIONS

OMNICEF (cefdinir) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS

BEFORE THERAPY WITH OMNICEF (CEFDINIR) IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFDINIR, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF CEFDINIR IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG β-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFDINIR OCCURS, THE DRUG SHOULD BE DISCONTINUED. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefdinir, and may range in severity from mild-to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

PRECAUTIONS

General

As with other broad-spectrum antibiotics, prolonged treatment may result in the possible emergence and overgrowth of resistant organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate alternative therapy should be administered.

Cefdinir, as with other broad-spectrum antimicrobials (antibiotics), should be prescribed with caution in individuals with a history of colitis.

In patients with transient or persistent renal insufficiency (creatinine clearance <30 mL/min), the total daily dose of OMNICEF should be reduced because high and prolonged plasma concentrations of cefdinir can result following recommended doses (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

Antacids containing magnesium or aluminum interfere with the absorption of cefdinir. If this type of antacid is required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

Iron supplements, including multivitamins that contain iron, interfere with the absorption of cefdinir. If iron supplements are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the supplement.

Iron-fortified infant formula does not significantly interfere with the absorption of cefdinir. Therefore, OMNICEF for Oral Suspension can be administered with iron-fortified infant formula.

If the patient is diabetic, he/she/the guardian should be aware that the oral suspension contains 2.86 g of sucrose per teaspoon.

Drug Interactions

Antacids: (aluminum- or magnesium-containing): Concomitant administration of 300-mg cefdinir capsules with 30 mL Maalox® TC suspension reduces rate (C_{max}) and extent (AUC) of absorption by approximately 40%. Time to reach C_{max} is also prolonged by 1 hour. There are no significant effects on cefdinir pharmacokinetics if the antacid is administered 2 hours before or 2 hours after cefdinir. If antacids are required during OMNICEF therapy, OMNICEF should be taken at least 2 hours before or after the antacid.

Probenecid: As with other β-lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 54% increase in peak cefdinir

FOR POSITION ONLY

EXHIBIT 3

APPROVAL LETTER

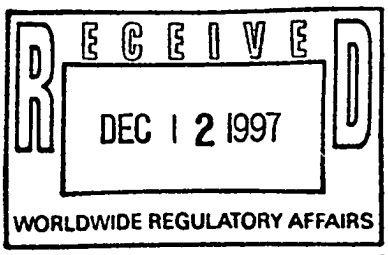
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-739
NDA 50-749

Parke-Davis
Attention: Drusilla Scott, Ph.D.
Director, Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48105



DEC 4 1997

Dear Dr. Scott:

Please refer to your new drug applications dated September 3, 1996 (NDA 50-739) and December 30, 1996 (NDA 50-749), received September 4, 1996 and December 31, 1996 respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omnicef (cefdinir) Capsules and Powder for Oral Suspension. We note that these products are subject to the exception provisions of Section 125 (2) of Title 1 of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated September 24, November 13, December 16, and December 31, 1996; and January 31, February 21, March 10, March 31, April 25, May 6, May 9, June 2, June 11, June 23, June 30, July 1, July 7, July 8, July 9, July 21, July 22, August 8, August 14, August 27, August 29, September 10, September 18, September 29, October 7, October 16, October 20, October 27, November 7, November 18, November 25, and December 3, 1997. The original User Fee goal date for these applications was September 4, 1997 (NDA 50-739) and December 31, 1997 (NDA 50-749). Your submission of June 23, 1997 extended the User Fee goal date for NDA 50-739 to December 4, 1997.

These new drug applications provide for treatment of patients with community-acquired pneumonia, acute exacerbations of chronic bronchitis, acute bacterial otitis media, acute maxillary sinusitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections.

We have completed the review of these applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the products with FPL that is not identical to this draft labeling may render the products misbranded and unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL

PRINTED LABELING" for approved NDA's 50-739, 50-749. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submissions dated October 20 and December 3, 1997. These commitments, along with any completion dates agreed upon, are listed below.

1. Adherence to regulatory specifications for the drug substance, regulatory specifications for the individual impurities in the cefdinir drug substance, regulatory specifications for the cefdinir 300 mg capsules, regulatory specifications for impurities, shelf-life, and stability commitments for the first three (3) production batches and annual batches as outlined in *CMC Attachment #1.*

2. Submission of the stability data for the first three (3) production batches of the capsules, when available.

3. Submission of dissolution profile results from 10 to 45 minutes for the three (3) NDA pilot batches of powder for oral suspension (lots D40115, D40116, and D40117) at 15 and 18 months. The dissolution test results (single point at 30 minutes) for commercial batches will be reported in the annual reports.

4. As per the GMP audit, the field office has recommended a 4% overage for the powder for oral suspension based on the audited data. The formal validation studies will have to justify any additional overage. Additional overage can be justified on the basis of validation data which should include in-process assays at all critical steps to account for the total manufacturing losses.

5. The pre-NDA lots TSK 04597, TSK 03897, and TSK 03797 can be used for supporting stability data by including testing which was not performed in the NDA batches. However, these batches can not be used for the post-approval commitment batches since these batches contain 7% overage.

6. Adherence to regulatory specifications for the cefdinir powder for oral suspension, regulatory specifications for related substances in the cefdinir powder for oral suspension, shelf-life, and the stability protocols as outlined in

CMC Attachment #2.

7. Submission of the stability data for the first three (3) productions batches of the powder for oral suspension, when available.

Protocols, data, and final reports should be submitted to your IND for these products and a copy of the cover letters sent to these NDA's. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to these NDA's as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to these applications, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Infective Drug Products and two copies of both the promotional material and the package inserts directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2120.

Sincerely yours,

David Feigal, M.D., M.P.H.
Acting Office Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURES

EXHIBIT 4

PATENT

United States Patent [19]

Takaya et al.

[11] Patent Number: 4,935,507

[45] Date of Patent: Jun. 19, 1990

[54] CRYSTALLINE 7-(2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO)-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER)

[75] Inventors: **Takao Takaya**, Kawanishi; **Fumiyuki Shirai**, Ikeda; **Hitoshi Nakamura**, Mino; **Yasunobu Inaba**, Toyonaka, all of Japan

[73] Assignee: **Fujisawa Pharmaceutical Co., Ltd.**, Osaka, Japan

[21] Appl. No.: **229,489**

[22] Filed: **Aug. 8, 1988**

[30] **Foreign Application Priority Data**

Aug. 19, 1987 [JP] Japan 62-206199

[51] **Int. Cl.**[5] **C07D 501/124**; A61K 31/545

[52] U.S. Cl. 540/222

[58] Field of Search 540/229, 222, 226; 514/202

[56] References Cited

U.S. PATENT DOCUMENTS

4,559,334 12/1985 Takaya et al. 514/202

Primary Examiner—Nicholas S. Rizzo

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

The invention relates to crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) useful as an antimicrobial agent.

5 Claims, 2 Drawing Sheets

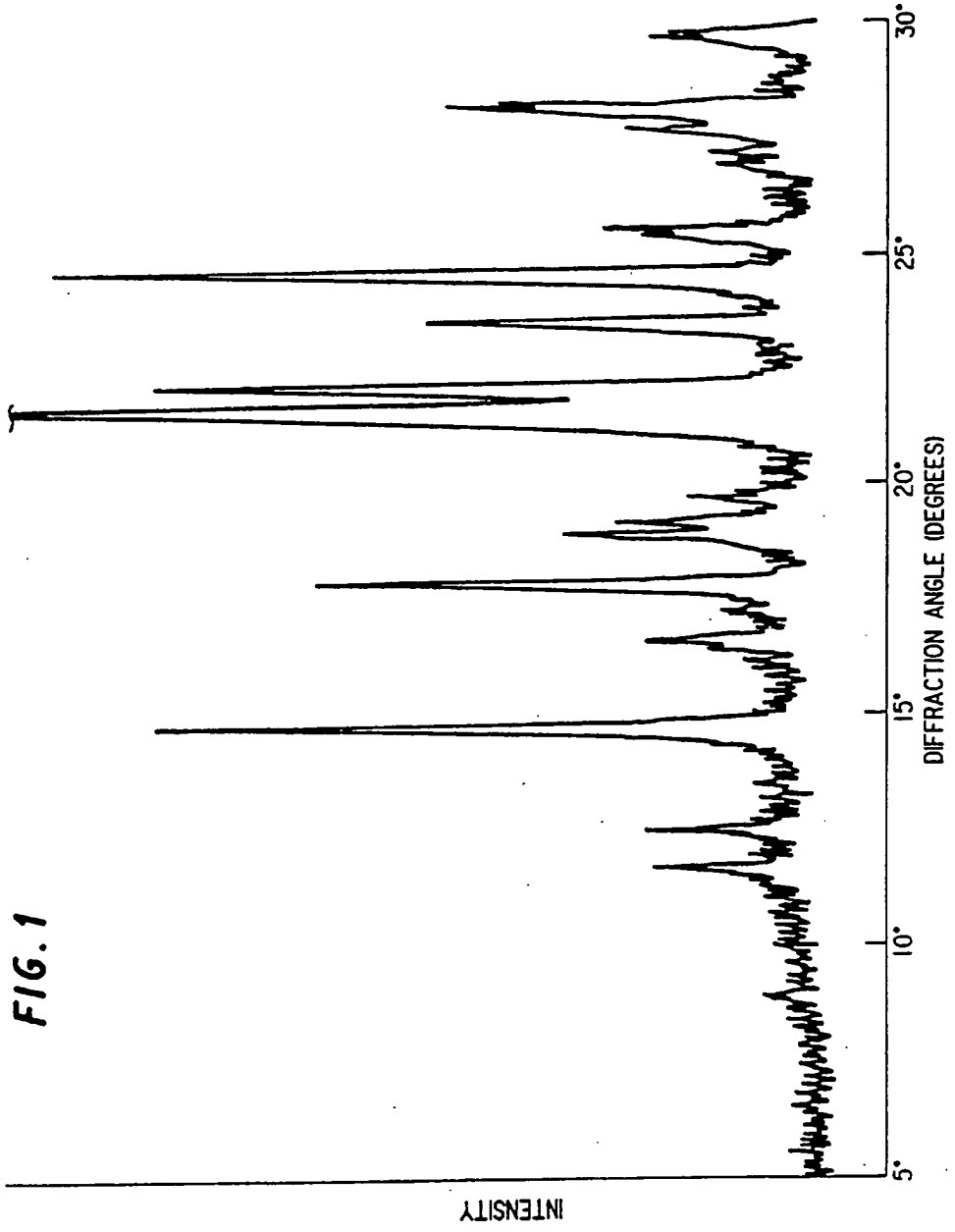


FIG. 1

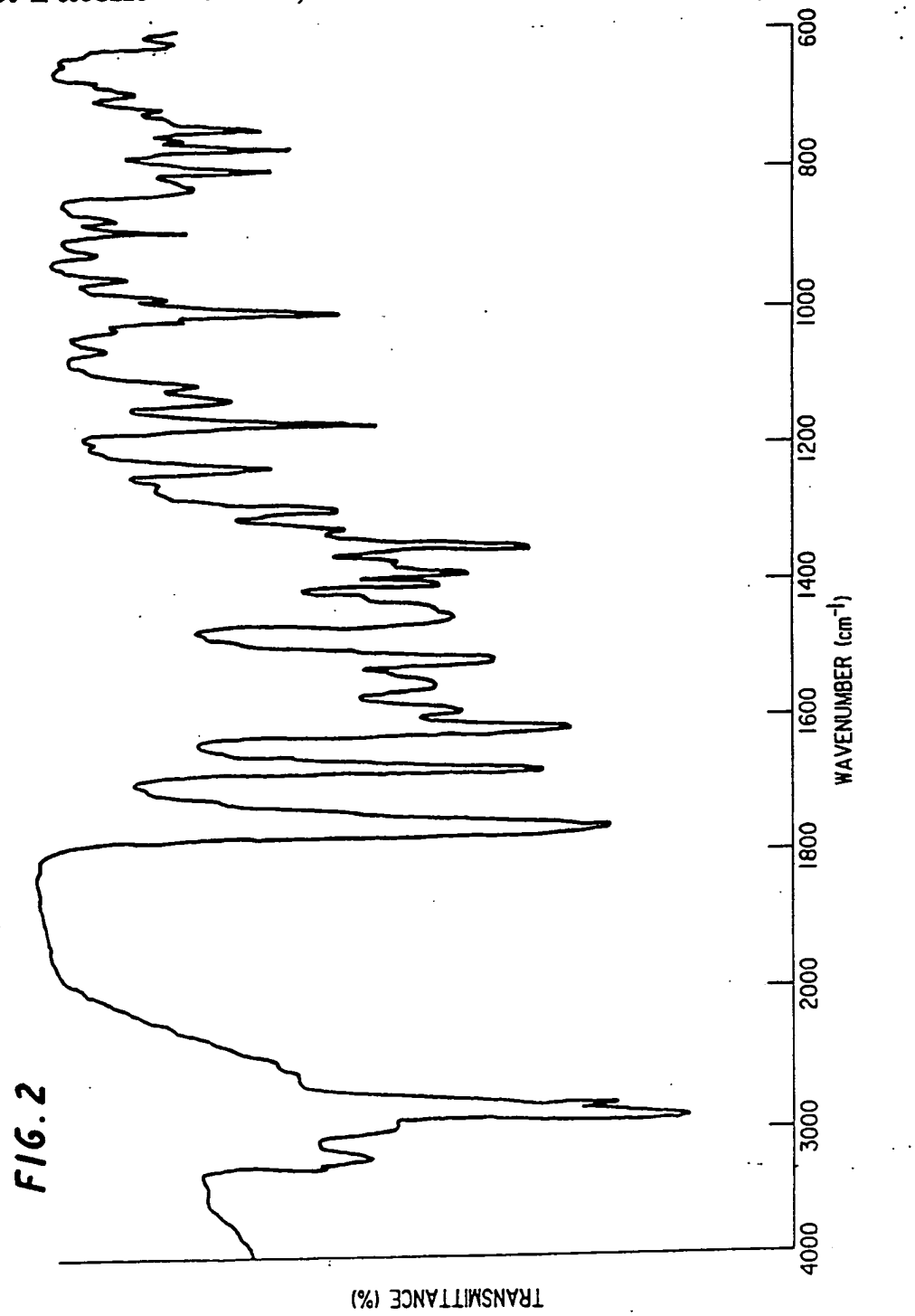
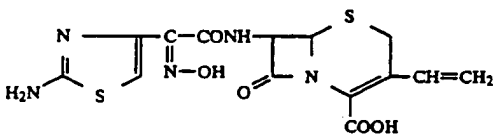

TRANSMITTANCE (%)
4000
3000
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER (cm⁻¹)

FIG. 2

CRYSTALLINE 7-(2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO)-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER)

The present invention relates to novel crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) [hereinafter referred to as "the compound (I)" in the present specification] as shown by the following formula (I):



(I)

The compound (I), which is a very useful antimicrobial agent, is a known compound and was described, for example, in U.S. Pat. No. 4,559,334 as the object compounds of Examples 14 and 16.

Our further experimental investigation revealed that the compound (I) each prepared according to the procedures of said Examples 14 and 16 in said U.S. Patent was a crystalline like amorphous product, not a crystalline product. However, the amorphous product has disadvantages that it is bulky, not so pure, unstable and insufficient in filtration rate, therefore it is not suitable for a pharmaceutical product or is not easy to handle in the pharmaceutical preparations, in producing it in a large scale or in storage.

After an intensive study, the inventors of the present invention succeeded in obtaining the compound (I) as a special crystalline form, i.e. Crystal A and completed the present invention, which is explained in detail as follows.

Physicochemical Properties of Crystal A of The Compound (I)

The physicochemical properties of Crystal A of the compound (I) provided by the present invention are explained in the following.

(1) Crystal Form

prisms

(2) Powder X-Ray Diffraction Pattern

Crystal A of the compound (I) shows its distinguishing peaks at the diffraction angles [$2\theta(°)$] as shown in the following table.

2θ (°)
about 14.7
about 17.8
about 21.5
about 22.0
about 23.4
about 24.5
about 28.1

In FIG. 1, a chart of powder X-ray diffraction pattern of Crystal A of the compound (I) obtained in Example 4 described later is shown.

But this diffraction pattern is given only for a reference and any crystal of the compound (I) which shows substantially the same diffraction pattern is identified as Crystal A of the compound (I).

(3) Infrared Absorption Spectrum

In FIG. 2, a chart of infrared absorption spectrum of Crystal A of the compound (I) obtained in Example 4 described later is shown.

But this spectrum is given only for a reference and any crystal of the compound (I) which shows substantially the same spectrum is identified as Crystal A of the compound (I).

The Process For Preparing Crystal A of The Compound (I)

In the following, the process for the preparation of Crystal A of the compound (I) of the present invention is explained in detail.

Crystal A of the compound (I) can be obtained by acidifying the solution containing the compound (I) at room temperature or under warming and thereby having the crystals separate out of the solution.

Suitable examples of "the solution containing the compound (I)" may include, for example, an aqueous solution of the alkali metal salt of the compound (I).

The solution containing the compound (I) is acidified, if necessary, after said solution is subjected to a column chromatography on activated charcoal, nonionic adsorption resin, alumina, acidic aluminium oxide. This acidifying process can be carried out by adding an acid such as hydrochloric acid or the like preferably in the temperature range from room temperature to 40° C., more preferably, from 15° to 40° C. The amount of the acid to be added is preferably the one which makes the pH value of the solution from 1 to 4.

Crystal A of the compound (I) can be also obtained by dissolving the compound (I) in an alcohol (preferably methanol), continuing to stir this solution slowly under warming (preferably below 40° C.), preferably after the addition of water warmed at almost the same temperature as that of said solution, then cooling this solution to room temperature and allowing it to stand.

During the crystallization of Crystal A, it is preferable to keep the condition of slightly beyond the saturation.

Crystal A of the compound (I) obtained according to aforesaid process can be collected by filtration and dried by means of the conventional methods.

The water content of Crystal A of the compound (I) obtained above is about 0.8% (measured by Karl Fisher method).

The Advantage of The Crystal A of The Compound (I)

The Crystal A of the compound (I) is not bulky, is very pure and is very stable against heat, light and the like. Therefore, the Crystal A of the compound (I) is suitable for a pharmaceutical product and is easy to handle in the pharmaceutical preparations and in storage.

Further, the Crystal A of the compound (I) has sufficient filtration rate and the operation efficiency in case of producing it is very high. Therefore the Crystal A of the compound (I) is very suitable to produce even in a large scale such as a laboratory scale.

Moreover, due to its ease to be filtered, impurities are difficult to mix in the purification step. Therefore, the compound (I) with high quality can be produced.

As stated above, the Crystal A of the compound (I) possesses very good advantage and much superior to the amorphous product of the compound (I).

In order to show said advantage of the Crystal A of the compound (I), the comparative test results on stability between the Crystal A of the compound (I) and the compound (I) given by aforesaid U.S. Pat. No. 4,559,334 are shown in the following.

Test Sample

Sample 1—the compound (I) obtained in Example 14 in said U.S. Patent

Sample 2—the compound (I) obtained in Example 16 in said U.S. Patent

Sample A—Crystal A of the compound (I) of the present invention

Test Method

The stability of each test sample was examined under the condition of 50° C. in a closed container.

Color of the solution of each sample was determined by measuring transmittance at 510 nm with spectrophotometer(T %) (1% solution in 1% $NaHCO_3$ aqueous solution was used).

The potency of each sample was determined by liquid chromatography and the residual percentage to the initial value was calculated.

Test Sample	Test Item	Test Results Initial	After 1 day	After 7 days
Sample 1	appearance	pale brownish yellow powder	pale brownish yellow powder	brownish yellow powder
	color of the solution(T%)	47.0	39.2	25.5
	potency (%)	100	97.2	85.1
Sample 2	appearance	yellow powder	yellow powder	brownish yellow powder

-continued

Test Sample	Test Item	Test Results Initial	After 1 day	After 7 days
	color of the solution(T%)	63.8	54.5	37.3
	potency (%)	100	89.3	52.4
Sample A	appearance	yellowish white crystal	yellowish white crystal	yellowish white crystal
	color of the solution(T%)	98.9	98.9	98.7
	Potency (%)	100	99.8	99.4

As shown in the test results, there was slight change in the appearance of Samples 1 and 2, while there was no change in the appearance of Sample A.

Further, there was significant lowering of the transmittance (T %) in case of Samples 1 and 2, while there was almost no lowering in case of Sample A.

These results indicated that Samples 1 and 2 were much easier to discolor than Sample A.

Further, as shown in the test results, the potency of Samples 1 and 2 apparently decreased, while the potency of Sample A was almost unchanged.

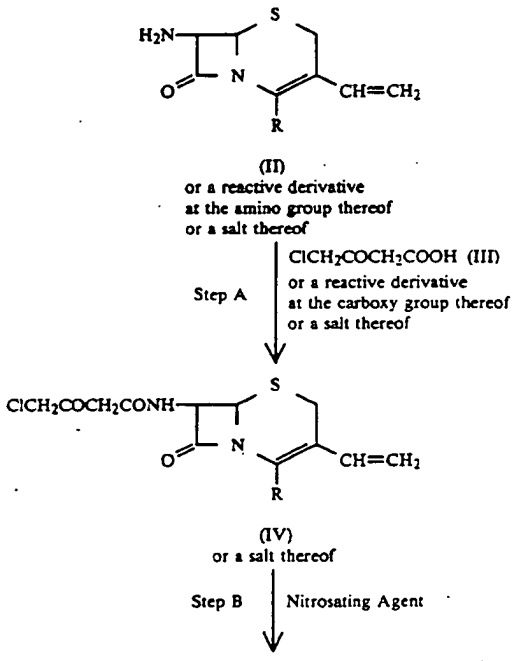
As stated above, only after 7 days there appeared much difference regarding the stability between the Crystal A of the compound (I) and the compound (I) given by U.S. Pat. No. 4,559,334.

Namely, it turned out that the Crystal A of the compound (I) was much superior to the compound (I) given by said U.S. Patent.

Next, the process for preparing the compound (I) used in the present invention is explained in detail.

Process For Preparing The Compound (I)

The compound (I) or a salt thereof can be prepared by the method disclosed in U.S. Pat. No. 4,559,334 as mentioned before, but in order to obtain the compound (I) at higher yield, it is preferable to use the method as shown in the following reaction schemes.



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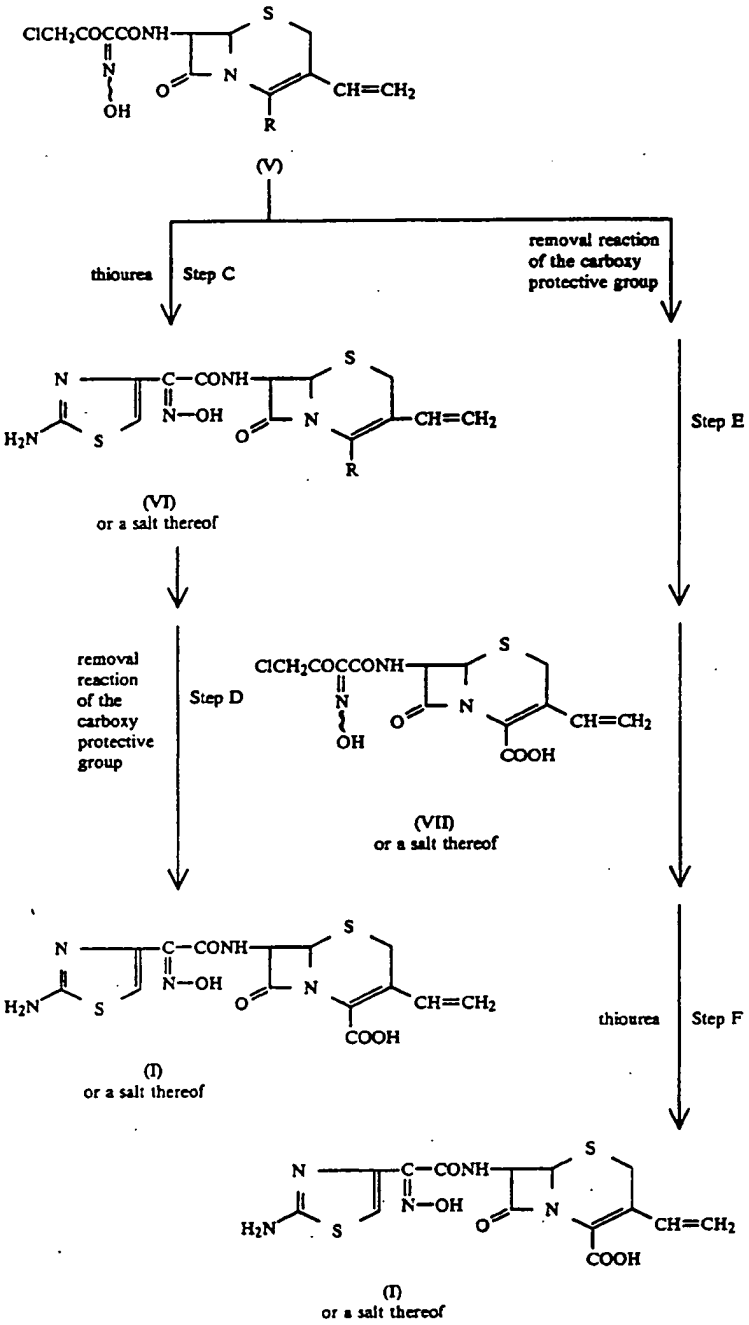

wherein R is a protected carboxy group.

Suitable "a protected carboxy group" in aforesaid R may include the ones which are used conventionally in cephalosporin compound, for example, esterified carboxy, and the like.

Suitable examples of said "esterfied carboxy" may include ar(loweralkoxycarbonyl such as benzyloxycarbonyl, benzhyeryloxycarbonyl, trityloxycarbonyl or the like, and the like.

Suitable salts of the compound (I) are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.) etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic acid addition salt, for example, an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); an organic phosphonic acid addition salt [e.g. 3-(N-formyl-N-hydroxyamino)-

propylphosphonate, 2-hydroxy-8-(N-hydroxyamino)-propylphosphonate, etc.], etc.; a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like.

The process for preparing aforesaid compound (I) is explained in detail in the following.

Step A

The compound (IV) or a salt thereof can be produced by reacting the compound (II) or a reactive derivative at the amino group thereof, or a salt thereof with the compound (III) or a reactive derivative at the carboxy group thereof or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include a conventional one, for example, a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as trimethylsilylacetamide, bis(trimethylsilyl)acetamide, bis(trimethylsilyl)urea, and the like, and suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide such as acid chloride, acid bromide, or the like, which can be prepared by the reaction of diketene and halogen.

Suitable salt of the compound (II) may include the acid addition salt as exemplified for the compound (I), and suitable salt of the compound (III) may include the same salt with a base as exemplified for the compound (I).

The reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, acetone, dioxane, acetonitrile, chloroform, benzene, carbon tetrachloride, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, pyridine, hexamethylphosphoramide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under cooling to warming.

Step B

The compound (V) can be produced by reacting the compound (IV) or a salt thereof with a nitrosating agent.

Suitable nitrosating agent may include nitrous acid and its conventional derivatives such as nitrosyl halide (e.g. nitrosyl chloride, nitrosyl bromide, etc.), alkali metal nitrite (e.g. sodium nitrite, potassium nitrite, etc.), alkyl nitrite (e.g. butyl nitrite, pentyl nitrite, isoamyl nitrite, etc.), and the like.

In case that a salt of nitrous acid, for example, its alkali metal salt is used as a nitrosating agent, the reaction is preferably carried out in the presence of an acid such as an inorganic or organic acid (e.g. hydrochloric acid, sulfuric acid, formic acid, acetic acid, etc.).

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, acetic acid, benzene, methanol, ethanol, tetrahydrofuran, methylene chloride, or a mixture thereof.

The reaction temperature is not critical and the reaction is preferably conducted within the range of cooling to an ambient temperature.

The compound (V) can be used as the starting compound in the next step, Step C, without isolation or purification.

Step C

The compound (VI) or a salt thereof can be produced by reacting the compound (V) with thiourea.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as ethyl acetate, methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane, water, acetic acid, formic acid, etc. or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under cooling to warming.

Step D

The compound (I) or a salt thereof can be produced by subjecting the compound (VI) or a salt thereof to the removal reaction of the carboxy-protective group.

Suitable salt of the compound (VI) may include the same acid addition salt as exemplified for the compound (I).

Suitable method for this removal reaction may include conventional one such as hydrolysis, reduction, or the like.

(i) For hydrolysis:

Hydrolysis is preferably carried out in the presence of an acid.

Suitable acid may be an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.), an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid, propionic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.), an acidic ion-exchange resin and the like. In case that the organic acid such as trifluoroacetic acid and p-toluenesulfonic acid is used in this reaction, the reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, etc.).

Further, instead of the above acid, Lewis acid such as boron trifluoride, boron trifluoride etherate, aluminum trichloride, antimony pentachloride, ferric chloride, stannic chloride, titanium tetrachloride, zinc chloride, and the like can be also used in this reaction, and in case of using Lewis acid, the reaction can preferably be carried out in the presence of cation trapping agent (e.g. anisole).

The hydrolysis is usually conducted in a conventional solvent which does not adversely influence the reaction such as methylene chloride, water, methanol, ethanol, propanol, tert-butyl alcohol, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane or a mixture thereof, and further the above-mentioned acids can be also used as a solvent when they are in liquid.

The reaction temperature of this hydrolysis is not critical, and the reaction is usually conducted under cooling to warming.

(ii) For Reduction:

Reduction is conducted in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal

platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like.

The reduction is usually conducted in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can be also used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually conducted under cooling to warming.

Step E

The compound (VII) or a salt thereof can be produced by subjecting the compound (V) to the removal reaction of the carboxy-protective group.

Suitable salts of the compound (VII) may include the same salt with a base as exemplified for the compound (I).

The removal reaction of the carboxy-protective group in this step can be carried out according to a similar manner to that explained in Step D.

Step F

The compound (I) or a salt thereof can be produced by reacting the compound (VII) or a salt thereof with thiourea.

This reaction can be carried out according to a similar manner to that explained in Step C.

In case that the compound (I) obtained by means of aforesaid process is in free form, it can be converted to its salt form, especially to its acid addition salt according to a conventional manner and in case that the compound (I) obtained is in salt form, it can be converted to its free form according to a conventional manner (Please make reference to References 1 to 4 described later).

Further, the compound (I) obtained according to aforesaid process can be converted to Crystal A of the present invention by applying the method to prepare said crystal disclosed before during the isolation step of the compound (I).

The process explained above in the one which gives the compound (I) in high yield and this process can be carried out very safely. Said process is also suitable for preparing the compound (I) in a large scale.

In the following, the present invention is explained in more detail according to Preparations and Examples.

Preparation 1

Benzhydryl 7-amino-3-vinyl-3-cephem-4-carboxylate hydrochloride (26.6 kg) was dissolved in N,N-dimethylacetamide (78 l) and then this solution was cooled to −10° C.

A solution of 4-chloroacetoacetyl chloride in methylene chloride, which was prepared by bubbling chlorine (6.5 kg) into a solution of diketene (7.6 kg) in methylene chloride (130 l) below −25° C., was added dropwise to the solution obtained above at −10°~0° C. with stirring. After the addition, the stirring was continued at the same temperature for 30 minutes.

After the reaction, the reaction mixture was diluted with methylene chloride (130 l) at 5° C. with stirring, then 6% sodium bicarbonate aqueous solution (260 l) was added thereto with stirring and then the organic layer was separated. The organic layer was washed with water (156 l) at 5° C. The organic layer was concentrated in vacuo to the volume of 182 l and then acetone (130 l) was added thereto and the solution was concentrated in vacuo again to the volume of 182 l. To the concentrated solution, acetone (78) was added and then methanol (130 l) was added dropwise at 20° C. After stirring for 10 minutes, water (260 l) was added thereto and this solution was cooled to 5° C. with stirring, then allowed to stand overnight.

The resultant crystals were collected by filtration, washed with 30% aqueous methanol (130 l) and then dried to give benzhydryl 7-(4-chloroacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (31.3 kg).

mp: 171° C.

IR (Nujol): 3260, 1775, 1713, 1661, 1224, 698 cm^{-1}.

NMR (DMSO-d_6, δ): 9.18 (1H, d, J=8 Hz), 7.6–7.1 (10H, m), 6.98 (1H, s , 6.76 (1H, dd, J=18 Hz and 11 Hz), 5.80 (1H, dd, J=8 Hz and 5 Hz), 5.63 (1H, d, J=18 Hz), 5.30 (1H, d, J=11 Hz), 5.22 (1H, d, J=5 Hz), 4.59 (2H, s), 3.93 and 3.60 (2H, ABq, J=18 Hz), 3.61 (2H, s).

Preparation 2

Benzhydryl 7-(4-chloroacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (30.8 kg) was suspended in methylene chloride (290 l) and this suspension was cooled to −5° C. After cooling, 10.6 N hydrogen chloride in tetrahydrofuran solution (267 ml) was added thereto, then isoamyl nitrite (7.1 kg) was added and the resultant mixture was stirred for 60 minutes at 0° C.

The resultant solution of benzhydryl 7-(4-chloro-2-hydroxyiminoacetoacetamido)-3-vinyl-3-cephem-4-carboxylate in methylene chloride was added to a solution of thiourea (6.5 kg) in N,N-dimethylacetamide (78 l) for 1 hour together with concentration of the reaction solution in vacuo. After methylene chloride was removed, the mixture was stirred for 30 minutes at 50° C. After the reaction was over, acetone (145 l) and 5% sodium bicarbonate aqueous solution (73 l) were added thereto at 20° C. and the resultant solution was added dropwise to water (290 l) for 20 minutes with keeping the temperature of the solution at 20° C. After this addition, the resultant solution was adjusted to pH 6 with 5% sodium bicarbonate aqueous solution, cooled to 5° C. with stirring and then allowed to stand overnight.

The resultant precipitates were collected by filtration, washed with 40% aqueous acetone (145 l) and dried to give benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem.-4-carboxylate (syn isomer)(36.9 kg).

IR (Nujol): 3320, 1782, 1720, 1670, 1618, 1528, 1220, 698 cm^{-1}.

NMR (DMSO-d_6, δ): 11.31 (1H, s), 9.58 (1H, d, J=8 Hz), 7.6–7.2 (10H, m), 7.14 (2H, broad s), 6.98 (1H, s), 6.79 (1H, dd, J=18 Hz and J=11 Hz), 6.72 (1H, s), 5.92 (1H, dd, J=8 Hz and 5 Hz), 5.67 (1H, d,J=18 Hz), 5.31

(1H, d, J=11 Hz), 5.29 (1H, d, J=5 Hz), 3.93 and 3.60 (2H, ABq, J=18 Hz).

Preparation 3

Benzhydryl 7-amino-3-vinyl-3-cephem.-4-carboxylate hydrochloride (68.9 g) and bis(trimethylsilyl)urea (103 g) were dissolved in tetrahydrofuran (700 ml) and the solution was cooled to −25° C. To this solution 4-chloroacetoacetyl chloride, which was obtained by reacting a solution of diketene (17.9 g) in methylene chloride (50 ml) with a solution of chlorine (14.9 g) in carbon tetrachloride (100 ml) at −40°~−30° C., was added slowly at −25° C. and the mixture was stirred for 1 hour at −15° C. The reaction mixture was poured into a mixture of ethyl acetate (900 ml) and water (900 ml). The organic layer was separated and washed with sodium chloride aqueous solution (700 ml). Solvent was removed and to the resultant crystals isopropyl ether (700 ml) was added and the mixture was stirred for 1 hour under ice-cooling. The crystals were collected by filtration and dried to give benzhydryl 7-(4-chloroacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (72.5 g).

NMR ($CDCl_3$, δ): 3.55 (2H, ABq, J=18 Hz), 3.60 (2H, s), 4.17 (2H, s), 4.99 (1H, d, J=5 Hz), 5.27 (1H, d, J=11 Hz), 5.42 (1H, d, J=17 Hz), 5.81 (1H, dd, J=5 Hz and 8 Hz), 6.95 (1H, s), 7.00 (1H, dd, J=11 Hz and 17 Hz), 7.10–7.53 (10H, m).

Preparation 4

To a solution of benzhydryl 7-(4-chloroacetoacetamido)-3-vinyl-3-cephem-4-carboxylate (5.0 g) in methylene chloride (45 ml) and acetic acid (16.5 ml) was added dropwise a solution of sodium nitrite (1.35 g) in water (2.5 ml) at −20° C. and then the mixture was stirred for 8 minutes. Ethyl acetoacetate (1.27 g) was added thereto and the mixture was stirred for 5 minutes, then the reaction solution was washed with water 3 times. The organic solvent was removed to give a residue, which was triturated with diisopropyl ether. The resultant solid was collected by filtration and dried to give benzhydryl 7-(4-chloro-2-hydroxyiminoacetoacetamido)-3-vinyl-3-cephem.-4-carboxylate (4.36 g).

IR (Nujol): 3260, 1765, 1705, 1650, 1540 cm^{-1}.

NMR ($CDCl_3$, δ): 3.60 (2H, broad s), 4.74 (2H, s), 5.09 (1H, d, J=5 Hz), 5.33 (1H, d, J=11 Hz), 5.49 (1H, d, J=17 Hz), 5.80 (1H, dd, J=5 Hz, and 8 Hz), 6.99 (1H, s), 7.10 (1H, dd, J=11 Hz and 17 Hz), 7.18–7.57 (10H, m), 9.38 (1H, d, J=8 Hz).

Preparation 5

Benzhydryl 7-(4-chloro-2-hydroxyiminoacetoacetamido)-3-vinyl-3-cephem.-4-carboxylate (25.0 g) was dissolved in a mixture of methylene chloride (150 ml) and anisole (15 ml). To the resultant solution was added dropwise 2,2,2-trifluoroacetic acid (500 ml) at 5° C. with stirring, then the mixture was stirred for 30 minutes.

The reaction solution was concentrated in vacuo and the resultant residue was triturated with diisopropyl ether (250 ml) to give a solid product (16.5 g). This product was dissolved in isopropyl alcohol (80 ml) and dealt with activated charcoal (1.6 g), then the solution was allowed to stand at 5° C. for 3 hours. The resultant precipitates were collected by filtration to give colorless crystals (7.8 g)(This crystal contains one molecule of isopropyl alcohol).

The resultant crystals (6.0 g) were recrystallized from a mixture of ethanol (25 ml) and water (50 ml) to give 7-(4-chloro-2-hydroxyiminoacetoacetamido)-3-vinyl3-cephem-4-carboxylic acid (3.4 g).

mp 134°–138° C. (decomp.).

IR (Nujol): 3350, 3450, 3250, 1770, 1700, 1665, 1540 cm^{-1}.

NMR (DMSO-d_6, δ): 3.83 and 3.57 (2H, ABq, J=18 Hz), 5.80 (2H, s), 5.17 (1H, d, J=5 Hz), 5.30 (1H, d, J=11 Hz), 5.57 (1H, d, J=17 Hz), 5.78 (1H, dd, J=8 Hz and J=5 Hz), 6.88 (1H, dd, J=17 Hz and J=11 Hz), 9.28 (1H, d, J=8 Hz), 13.08 (1H, s).

The Preparation Of Crystal A Of The Compound (I)

EXAMPLE 1

7-[2-(2-Aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem.-4-carboxylic acid (syn isomer)(an amorphous product)(29.55 g) was added to water (300 ml) and the mixture was adjusted to pH 6.0 with saturated sodium bicarbonate aqueous solution. The resultant solution was subjected to a column chromatography on activated charcoal and eluted with 20% aqueous acetone. The fractions were combined and concentrated to a volume of 500 ml. The resultant solution was adjusted to pH 1.8 at 35° C. with 4N hydrochloric acid. The resultant precipitates were collected by filtration, washed with water and dried to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(19.29 g) as crystals (Crystal A).

IR (Nujol): 1760, 1670, 1620 cm^{-1}.

EXAMPLE 2

To a solution of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(an amorphous product)(0.5 g) in methanol (10 ml) was added dropwise warm water (35° C.; 1.5 ml) at 35° C. and the resultant solution was stirred slowly for 3 minutes, then allowed to stand at room temperature. The resultant crystals were collected by filtration, washed with water and then dried to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) as crystals (Crystal A)(0.4 g).

IR (Nujol): 1760, 1670, 1620 cm^{-1}.

In the following, powder X-ray diffraction pattern of this Crystal A was shown.

The measurement condition was as follows.

Target: Cu	Filter: Ni
Voltage: 30 kv	Current: 10 mA
Detector: Scintillation Counter	

2 θ(°)	relative intensity
11.7	18
12.5	15
14.7	76
16.6	16
17.8	56
18.9	22
19.1	16
21.5	100
22.0	70
23.4	38
24.4	80
25.3	22
26.9	10
27.6	22
28.0	40

-continued

29.6	18

EXAMPLE 3

Benzhydryl 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer)(35 kg) was suspended in anisole (239 l) and this suspension was cooled to −10° C. 98% formic acid (3.3 kg) and 47% boron trifluoride etherate (54 kg) were added thereto at the same temperature, then the mixture was stirred for 40 minutes at −1°~1° C.

To the reaction solution, acetone cooled to −10° C. (199 l) was added. By adding dropwise both this solution and 12% sodium hydroxide aqueous solution to a mixture cooled at −10° C. of water (265) and acetone (212 l) at the same time with stirring, the neutralization reaction was carried out in the range from pH 4 to 6 at −10°~0° C.

After neutralization, the mixture was allowed to stand, then aqueous layer was separated. Aqueous layer was washed with ethyl acetate (106 l). After the aqueous layer was washed with ethyl acetate (106 l) again, it was concentrated in vacuo to the volume of 557 l. The concentrated solution was adjusted to pH 3.7 with 17.5% hydrochloric acid at 20° C. to precipitate the crystals. This mixture was cooled to 5° C. with stirring, then stirred overnight. The resultant crystals were collected by filtration, washed with water (133 l) and dried to give crude crystals of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(Crystal A)(17.3 kg).

IR (Nujol): 3295, 1767, 1683, 1620, 1518, 1013 cm^{-1}.

NMR (DMSO-d_6, δ) 11.27 (1H, broad s , 9.53 (1H, d, J=8 Hz), 7.11 (2H, broad s), 6.96 (1H, dd, J=18 Hz and 11 Hz), 6.70 (1H, s), 5.80 (1H, dd, J=8 Hz and 5 Hz), 5.60 (1H, d, J=18 Hz), 5.31 (1H, d, J=11 Hz), 5.20 (1H, d, J=5 Hz), 3.87 and 3.53 (2H, ABq, J=18 Hz).

EXAMPLE 4

A suspension of crude crystals of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl3-cephem-4-carboxylic acid (syn isomer)(Crystal A) obtained in aforesaid Example 3 (21.1 kg) in water (255 l) was cooled to 5° C. Sodium bicarbonate (2.7 kg) was added thereto at 5° C. and dissolved under reduced pressure with degassing. The resultant solution was subjected to a column chromatography on nonionic adsorption resin "Diaion HP-20" (51 l) Trademark:manufactured by Mitsubishi Chemical Industries). The eluate obtained above was then subjected to a column chromatography on γ-alumina (25.5 l) and eluted with 3% sodium acetate aqueous solution. The resultant eluate was adjusted to pH 3.5 at 21°-25° C. with 17.5% hydrochloric acid and then the crystals were crystallized out of the solution by the addition of 17.5% hydrochloric acid with keeping the pH of the solution at 3.5. The resultant suspension containing the crystals was cooled to 5° C. and stirred overnight. The crystals were collected by filtration, washed with water (42.5 l) and dried in vacuo at 35° C. to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(6.7 kg) as crystals (Crystal A).

IR (Nujol): 1765, 1685, 1620 cm^{-1}.

In the following, powder X-ray diffraction pattern of this Crystal A was shown. The measurement condition was the same that was used in Example 2.

2 θ (°)	relative intensity
11.8	15
12.6	16
14.7	66
16.6	16
17.8	49
18.9	24
19.2	18
21.5	100
22.0	66
23.4	38
24.5	77
25.4	20
26.9	8
27.7	18
28.1	36
29.7	15

EXAMPLE 5

7-(4-Chloro-2-hydroxyiminoacetoacetamido)-3-vinyl-3-cepham-4-carboxylic acid (373.8 mg) was added to a mixture of thiourea (76 mg), sodium acetate (82 mg) and water (5 ml). The pH value of the reaction mixture was maintained from 5.5 to 5.7 during the reaction by the addition of 1.4% ammonium hydroxide aqueous solution. The reaction mixture was stirred at room temperature for 4 hours, then thiourea (38 mg) was added thereto and the mixture was stirred further for 2 hours.

The yellowish reaction mixture was filtered by passing it through a column packed with acidic aluminium oxide (5.0 g) [Elution was carried out by using 1% sodium acetate buffer solution (pH 6.0)]. The eluate was adjusted to pH 3.3 with 10% hydrochloric acid, then stirred slowly for 1 hour at room temperature. The resultant crystals were collected by filtration, washed with small amount of cold water and dried in vacuo over phosphorus pentoxide to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4carboxylic acid (syn isomer) as crystals (Crystal A) (239 mg)

mp: 182°-187° C. (decomp.).

IR (Nujol): 3350, 3300, 1770, 1690, 1630, 1600, 1560, 1520 cm^{-1}.

NMR (DMSO-d_6, δ): 3.57 and 3.83 (2H, ABq, J=18 Hz), 5.18 (1H, d, J=5 Hz), 5.33 (1H, d, J=11 Hz), 5.60 (1H, d, J=17 Hz), 5.80 (1H, dd, J=8 Hz and J=5 Hz), 6.70 (1H, s), 7.03 (1H, dd, J=11 Hz and J=17 Hz), 7.08 (2H, broad s), 9.43 (1H, d, J=8 Hz).

In the following References 1 to 4, the various salts of the compound (I) are given.

Reference 1

To a suspension of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(4.26 g) in water (26 ml) was added conc. hydrochloric acid (4.26 ml) at room temperature, then the mixture was stirred under ice-cooling for 1 hour. The solvent was removed by decantation and resultant oily precipitates were triturated with diethyl ether, acetone and n-hexane. The resultant powder was collected by filtration to give 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid hydrochloride (syn isomer)(4.30 g).

IR (Nujol): 3200, 1760–1780, 1720, 1660–1680, 1625 cm^{-1}.

NMR (DMSO-d_6, δ): 3.70 (2H, ABq, J=18 and 26 Hz), 5.22 (1H, d, J=5 Hz), 5.30 (1H, d, J=11 Hz), 5.75

(1H, dd, J=8 and 5 Hz), 5.59 (1H, d, J=17 Hz), 6.85 (1H, s), 6.70–7.17 (2H, m), 9.67 (1H, d, J=8 Hz), 12.3 (1H, broad s).

Reference 2

To a suspension of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(0.4 g) in ethyl acetate (2 ml) and ethanol (2 ml) was added ethyl acetate solution containing sulfuric acid at 10% (0.54 ml) under ice-cooling, then the reaction mixture was stirred under ice-cooling for 1 hour. To the reaction mixture was added diethyl ether (40 ml) and the mixture was further stirred under ice-cooling for 1 hour. The resultant precipitates were collected by filtration, washed with diethyl ether and dried in vacuo to give sulfuric acid salt of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(0.48 g).

IR (Nujol): 1765, 1750, 1720, 1660, 1640 cm^{-1}.

NMR (DMSO-d_6, δ): 3.73 (2H, ABq, J=18 Hz and 26 Hz), 5.21 (1H, d, J=5 Hz), 5.0–5.90 (3H, m), 6.89 (1H, s), 6.70–7.17 (2H, m), 9.69 (1H, d, J=8 Hz).

Reference 3

To a suspension of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(0.5 g) in methanol (2 ml) was added a solution of methanesulfonic acid (0.158 g) in methanol (0.5 ml) at 0°–5° C., then the mixture was stirred at the same temperature for 1 hour. The reaction mixture was added dropwise to ethanol and the resultant precipitates were collected by filtration to give methanesulfonic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) (0.56 g).

IR (Nujol): 1760–1780, 1630–1670, 1590, 1520 cm^{-1}.

NMR (DMSO-d_6, δ) 2.40 (3H, s), 3.72 (2H, ABq, J=18 Hz and 26 Hz), 5.22 (1H, d, J=5 Hz), 5.30 (1H, d, J=11 Hz), 5.59 (1H, d, J=17 Hz), 5.60–5.90 (1H, m), 6.86 (1H, s), 6.67–7.17 (2H, m), 9.67 (1H, d, J=8 Hz), 12.2 (1H, broad s).

Reference 4

To an aqueous solution (40 ml) of 3-(N-formyl-N-hydroxyamino)propylphosphonic acid (0.43 g) was added 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (1.0 g) with vigorous stirring, then the mixture was stirred at room temperature for 5 hours. The reaction mixture was lyophilized to give a hygroscopic solid. This solid was dissolved in methanol (10 ml), then the resultant solution was added dropwise to diethyl ether (500 ml) under cooling. The resultant precipitates were collected by filtration to give 3-(N-formyl-N-hydroxyamino)propylphosphonic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)(0.50 g) as powder.

NMR (D_2O, δ): 1.39–2.20 (4H, m), 3.47–3.87 (4H, m), 5.27 (1H, d, J=5 Hz), 5.30–5.73 (2H, m), 5.80 (1H, d, J=5 Hz), 6.95 (1H, dd, J=17 Hz and J=20 Hz), 7.11 (1H, s), 7.94, 8.29 (total 1H, each s).

What we claim is:

1. Crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem.-4-carboxylic acid (syn isomer) which shows the peaks at the diffraction angles shown in the following table in its powder X-ray diffraction pattern:

diffraction angle(°)
about 14.7
about 17.8
about 21.5
about 22.0
about 23.4
about 24.5
about 28.1

2. Crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which is obtainable by acidifying a solution containing 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) at room temperature or under warming.

3. Crystalline substance of claim 2, wherein a solution containing 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) is an aqueous solution of an alkali metal salt of said compound.

4. Crystalline substance of claim 3, wherein the acidifying of the solution is carried out at the temperature from room temperature to 40° C. at the pH from 1 to 4.

5. Crystalline 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) which is obtainable by dissolving 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer) in an alcohol, continuing to stir the solution slowly under warming, then cooling the solution to room temperature and allowing the solution to stand.

* * * * *

EXHIBIT 5

MAINTENANCE FEE RECEIPTS

Patent Maintenance Fees - Public Inquiry

Patent#: 4935507 Filed: 08/08/88 Issued: 06/19/90 Serial#: 07229489
Status: 12th Year Fee Window Opens: 06/19/01 Sml Entity: NO
Window Opens: 06/19/01 Surchg Due: 12/19/01 Expiration: 06/19/02
Fee Amt Due:$ 3160 Surchg Amt Due:$ Total Amt Due:$ 3160
Fee Code: 185 Surchg Code:
Title: CRYSTALLINE 7-(2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO)-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER)

Address For Fee Purposes:
COMPUTER PATENT ANNUITIES
901 N. WASHINGTON STREET
SUITE 305
ALEXANDRIA VA 22314

Most Recent Significant Events:

09/25/97	Payment of Maintenance Fee, 8th Year, Large Entity
11/29/93	Payment of Maintenance Fee, 4th Year, Large Entity
02/01/91	Payor Number Assigned
	Last Event On Maintenance History

EXHIBIT 6

IND SUBMISSION LETTER

PARKE-DAVIS
Pharmaceutical Research Division
Warner-Lambert Company

April 30, 1990

Serial No. 000
CI-983 Capsules

Re: Original IND

Food and Drug Administration
Center for Drug Evaluation
and Research
Central Document Room
12420 Parklawn Drive
Park Building, Room 214
Rockville, Maryland 20852

Dear Sir or Madam:

Pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 312.20, an Investigational New Drug Application for CI-983 Capsules, a cephalosporin antibacterial agent, is submitted in triplicate.

Warner-Lambert has licensed CI-983 from Fujisawa Pharmaceutical Company, Osaka, Japan. A marketing application was submitted in Japan in December 1989 and is under review.

The initial work to be done under this IND will be a Phase 1 study in the United States. CI-983 Capsules will not be administered to humans before 30 days from the official date of receipt of this submission.

If there are any questions or comments on this submission, please contact me at (313) 996-1819, or Dr. Howard Holden at (313) 996-5141.

Sincerely,

Drusilla Scott

Drusilla L. Scott, Ph.D.
Manager, Worldwide Regulatory Affairs

220901.bf

Attachments

PD/WL Distribution
F.A. de la Iglesia
R. Guttendrof
L. McKay
L. Paradiso
D. Scott
A. Vassos
CBI *
RA, AA, CI-983 File IND 34,738 *

* with attachment

April 11, 1991

IND 34,738
Serial No. 031
CI-983 Capsules

Re: Protocol Amendment:
New Protocol
Change in Protocol
Information Amendment:
Pharmacology/Toxicology

Murray Lumpkin, M.D.
Director
Division of Anti-Infective Drug
Products (HFD-520)
Document Control Room 12B-30
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Lumpkin:

We hereby notify you of a clinical study to be conducted in accordance with the attached Protocol 983-021-0 entitled "A Single-Dose Pharmacokinetic Study Comparing The Bioavailability Of Parke-Davis CI-983 Capsules And Parke-Davis CI-983 Pediatric Suspension To That Of Fujisawa CI-983 Capsules."

This study will be conducted in healthy subjects at the Parke-Davis Community Research Clinic. While the protocol specifies that each subject will receive a single 200 mg dose of each of the three formulations, it has been amended to specify a 400 mg dose. This higher dose will help ensure that the pharmacokinetic parameters can be accurately and reproducibly characterized. This amendment follows the protocol in this submission.

An abbreviated information amendment that describes the suspension follows the protocol and amendment. An abbreviated amendment describing the Parke-Davis capsule was submitted to the IND on March 26 (Serial No. 028), and detailed information on the Fujisawa capsule was submitted in the original IND. Detailed amendments on the Parke-Davis capsule and suspension are in preparation for submission in the near future.

Also attached are four toxicology research reports:

"Five-Week Oral Toxicity Study Of Cefdinir In Infants Rats" dated March 14, 1991 (Research Report No. 745-01748).

"Four-Week Oral Toxicity Study Of Cefdinir In Infant Dogs" dated March 14, 1991 (Research Report No. 745-01749).

"Acute Toxicity Study Of Cefdinir In Infant Rats" dated March 14, 1991 (Research Report No. 745-01750).

"Acute Toxicity Study Of Cefdinir In Infant Dogs" dated March 14, 1991 (Research Report No. 745-01751).

These studies in infant animals are submitted as part of the documentation required to support pediatric studies.

If there are further questions or comments, please call me at (313) 996-1819 [Fax (313) 996-7890] or Dr. Howard Holden at (313) 996-5141.

Sincerely,

Drusilla L. Scott, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

DLS:bb/41091.031

Attachments

Warner-Lambert Distribution

G. Anthony (MOPS)
J. Boonstra* (MOPS)
S. Brennan
P. Chen
H. Holden
E. Lewis (MOPS)
M. McKenna
D. Scott
CBI, AA*
R.A., AA CI-983 IND File 34,738*

*with attachment

September 19, 1991

IND 34,738
Serial No. 060
Cefdinir Capsules

Re: Information Amendment
Chemistry, Manufacturing
and Controls

Murray Lumpkin, M.D.
Director
Division of Anti-infective Drug
Products (HFD-520)
Document Control Room 12B-30
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fisher Lane
Rockville, Maryland 20857

Dear Dr. Lumpkin:

Attached is an information amendment (Research Report No. REG 956-00113) to our IND 34,738, updating the Chemistry, Manufacturing and Controls for Cefdinir powder for oral suspension.

In the IND amendment of April 11, 1991 (Serial No. 031), an oral suspension formulation of Cefdinir was described. This formulation was used in Parke-Davis Study 983-021-0 to determine its relative bioavailability to Cefdinir Capsules.

On August 13, 1991, the IND was amended (Serial No. 51) to provide for a revised formulation. In the amendment, a brief description of the manufacturing and controls for the revised formulation were provided. At that time a commitment was made to provide a detailed manufacturing and controls section.

This amendment (Research Report No. REG 956-00113) provides the detailed information on the manufacturing and controls for the revised formulation. The same specifications as described in the IND amendment, Serial No. 031, are used to control the performance of the suspension. All the testing results demonstrate that the two formulations behave the same in vitro.

The Cefdinir powder for oral suspension is manufactured by Parke-Davis in our Rochester, Michigan facility. The stability of this powder for oral suspension will be followed for the planned duration of the proposed clinical studies according to the protocol provided.

We would appreciate your adding this amendment to our IND file. If you have any additional questions or comments, please call me at (313) 996-7596.

Sincerely,

Sean Brennan

Sean Brennan, Ph.D.
Associate Director
Worldwide Regulatory Affairs

SB:bb/91991.060

Attachment

PARKE-DAVIS
Pharmaceutical Research Division
Warner-Lambert Company

October 10, 1991

IND 34,738
Serial No. 065
CI-983 Capsules

Re: Response to FDA Request
for Information

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug
Products (HFD-520)
Document Control Room 12B-30
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Lumpkin:

Reference is made to our IND # 34,738 for CI-983 capsules, to your letter of May 28, 1991, to our letters to the IND of July 10, 1991, August 15, 1991 and September 19, 1991, and to phone discussions with Dr. Linda Sherman of your Division on October 7 and 8, 1991.

As requested by Dr. Sherman, we are providing brief summaries of our previously submitted responses to the questions addressed to us on page 6 (Item 6) in your letter of May 28, 1991 dealing with the data requested to support clinical studies in the pediatric population. The summaries are presented as follows:

1. Summary of all available Cefdinir adult safety data
2. Summary of all Cefdinir data from Japanese pediatric studies
3. Summary of adult Japanese, British, and US pharmacokinetic data on Cefdinir
4. Summary of Cefdinir protein binding, PK parameters, safety and comparability of the capsule and the suspension, and bioavailabilty of the suspension in adults
5. Summary of chemistry and manufacturing control of the Cefdinir suspension
6. Summary of all juvenile animal toxicity studies on Cefdinir.

It is our understanding that these summaries will be utilized for internal discussion to review our submissions.

If there are any questions on this submission, please contact me at (313) 996-5141 (Fax (313) 996-7890) or Dr. Drusilla Scott at (313) 996-1819.

Sincerely yours,

Howard T. Holden

Howard T. Holden, Ph.D.
Director
Worldwide Regulatory Affairs

HTH:bb/10991.065

Attachment - Desk copy for Dr. Sherman

EXHIBIT 7

IND ACKNOWLEDGMENT LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 34,738

Date MAY 8 1990

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 481052430

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 34,738

Sponsor: Parke-Davis Pharmaceutical Research

Name of Drug: CI-983

Date of Submission: April 30, 1990

Date of Receipt: May 2, 1990

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations) Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows.

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-520)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Kathy Huntley Consumer Safety Officer at (301) 443-0257.

Sincerely yours,

for Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-520 - yellow
HFD-520/CSO - green

IND ACKNOWLEDGEMENT

EXHIBIT 8

NDA SUBMISSION LETTER

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

December 30, 1996

NDA 50-749
Ref. No. 1
Omnicef™ (cefdinir) for Oral Suspension

Re: Original New Drug Application
User Fee I.D. No. 2566

Food and Drug Administration
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

Dear Sir/Madam:

In accordance with Section 507 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, Parke-Davis is submitting a New Drug Application (NDA) for Omnicef™ (cefdinir) for Oral Suspension for the treatment of mild to moderate bacterial infections in an outpatient setting. The number NDA 50-749 was preassigned on November 25, 1996.

As required by the Prescription Drug User Fee Act, 50% of the 1996 application fee ($102,000) was sent to the Food and Drug Administration in care of Mellon Bank, Pittsburgh, Pennsylvania on December 20, 1996. A copy of the user fee transmittal letter and cover sheet are attached; our Identification Number is 2566. As stated in the December 23, 1996 publication of 1997 user fees (61 FR 67557), we understand that we will be billed for the 1997 increase since this application is being submitted by December 31, 1996.

This submission includes an archival copy of the NDA (10 volumes) and review copies for each technical reviewer. A field copy of Item 3 (Chemistry, Manufacturing, and Controls) has been sent to the FDA District Office in Newark, New Jersey in accordance with 21 CFR 314.440(a)(4). A field copy has also been sent to the district office in San Juan since the product will be manufactured by our contractor, Eli Lilly, in its Carolina, Puerto Rico facility.

Patent information and certification for the Generic Drug Enforcement Act in Item 13 are located in Volume 1.1, immediately preceding Item 1, NDA Index.

NDA 50-739 for Omnicef™ (cefdinir) Capsules, 300 mg, was submitted on September 3, 1996. That NDA described the cefdinir capsule formulation and contained all the clinical and preclinical studies that support the approval of both the adult and pediatric indications requested. Therefore, NDA 50-739 should be referenced for that information.

NDA 50-749 consists primarily of the following components: a comprehensive summary (Item 2), a description of chemistry manufacturing, and controls for the suspension formulation (Items 3 & 4), a report on a bioequivalence study between the market-image suspension and that used in clinical trials (Items 6 and 8), and a rationale for the approval of an acute sinusitis indication in the pediatric population, based on the provisions of 21 CFR 201.57(f)(9)(iv) (Item 8).

The NDA is available as an electronic regulatory submission as well as a paper copy; the features are described in Item 2.1, NDA Overview. The electronic and paper versions differ in that the electronic version has no title (cover) pages and the NDA page number is not visible. However, documents can be retrieved by hyperlinks from the table of contents.

If there are any questions or comments regarding the NDA, please contact me at 313/996-1819 or Dr. Tim Cunniff at 313/996-7091, FAX 313/998-3283. Dr. Sean Brennan may be contacted for issues related to chemistry, manufacturing and controls at 313/996-7596, or Dr. Paul Chen at 313/996-2623, FAX 313/996-7890.

Sincerely,

Drusilla L. Scott, Ph.D.
Director, FDA Liaison
Worldwide Regulatory Affairs

DS:rm t:\nda\50-739\123096.001

Attachments

NDA Copies

"Blue" Archive	Vol. 1.1 - 1.10
"Red" Chemistry	Vol. 1.1 - 1.6
"Orange" Biopharmaceutics	Vol. 1.1, 1.7-1.8
"Tan" Medical	Vol. 1.1, 1.9 - 1.10
"Maroon" Field (Newark) Ms. Regina Brown	Vol. 1.2 - 1.5
"Maroon" Field (San Juan) Mr. Samuel Jones/Mr. Richard Dent	Vol. 1.2 - 1.5

EXHIBIT 9

NDA RECEIPT LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-749

JAN 10 1997

Attention: Drusilla L. Scott, Ph.D:
Parke- Davis Pharmaceutical Research
2800 Plymouth Road
P.O. Box 1047
Ann Arbor, Michigan 48106-1047

Dear Dr. Scott:

We have received your new drug application (NDA) submitted under section 507 of the Federal Food, Drug and Cosmetic Act for the following:

Name of drug Product: Omnicef (cefdinir) for Oral Suspension

Therapeutic Classification 3S

Date of Application December 30, 1996

Date of Receipt: December 31, 1996

Our Reference Number: NDA 50-749

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 507 of the Act in accordance with 21 CFR 314.101(a).

Should you have any questions, please call: Carmen DeBellas
Project Manager
301-827-2125

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

James D. Bona, R.Ph., M.P.H.
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

EXHIBIT 10

IND LOG

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic:

Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B04128	0	Mon, Apr 30, 1990	Initial IND
			Volumes = 6 Item 1: Cover Sheet Item 2: Table of Contents Item 3: Introductory Statement Item 4: General Investigational Plan Item 5: Investigator's Brochure: RR-X 720-02745 Item 6: Protocol and Related Information PR. 983-001: A. Sedman, MD/E. Posvar, MD/A. Vassos, MD Item 7: Chemistry, Manufacturing and Controls Item 8: Microbiology, General Pharmacology, Pharmacokinetics and Toxicology (57) Research Reports submitted. Refer to Research Report list for RR #, date, author and title. Item 9: Previous Human Experience (3) Research Reports submitted. Refer to Research Report list for RR #, date, author and title. Item 10: Additional Information
B04133		Tue, May 08, 1990	FDA Letter RE: Acknowledging Receipt (IND 34,739)
			RE: Acknowledgement of receipt of IND on 8-May-90; Number 34,738 assigned.
		FDA	
B04133	1	Fri, Jun 08, 1990	Protocol Amendment (Change in Protocol)
			Amendment #1: PR. 983-001-000: 08-Jun-90: Provides revisions: 1. 800 MG not to be administered 2. Subjects to keep dialy diary 3. Additional 10CC blood to be withdrawn 4. If blood donated 2 months prior subject excluded 5. Asprin-containing or non-steroidal anti-inflammatory drugs prohibited two weeks prior to start of study 6. History of lactose intolerance, subjects excluded
B04133	2	Wed, Aug 15, 1990	Protocol Amendment (Change in Protocol)
			Amendment #2: PR. 983-001-000: 08-Aug-90: An additional determination of complete blood count.
B04133	3	Thu, Sep 06, 1990	Information Amendment (Pharmacology/Toxicology)
			(3) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04134	4	Fri, Sep 14, 1990	Letter RE: Investigator's Brochure
		M. Lumpkin, MD	CI-983 RE: Revised version of Investigator's Brochure that includes the results from segment II and III reproductive toxicity studies and will be provided to future investigators who evaluate this drug.

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B04134	5	Mon, Sep 24, 1990	Letter RE: Request for Meeting with FDA CI-983 RE: Request a meeting with the agency to discuss our proposed clinical development plan. The plan is attached, following a proposed meeting agenda and issues for discussion. Also attached; we would not discuss these at meeting, but are provided for background. 1. Copies of the planned protocol for the initial efficacy studies 2. A dose-range finding study in respiratory tract infection 3. Two urinary tract infection studies
B04134	6	Mon, Oct 01, 1990 M. Lumpkin, MD	Letter RE: Chemistry, Manufacturing & Controls RE: CI-983-018-000 Updated Chemistry, Manufacturing & Controls; regarding our #2 capsules.
B04134	7	Thu, Oct 11, 1990	Information Amendment (Clinical) (1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04135	8	Thu, Oct 18, 1990	Information Amendment (Pharmacology/Toxicology) (1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.

Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04135	9	Thu, Oct 25, 1990		Protocol Amendment (New Investigators)
				PR. 983-002-001:
				PR. 983-002-002:
				PR. 983-002-003:
				PR. 983-002-006:
				PR. 983-002-008:
				PR. 983-002-009:
				PR. 983-002-010:
				PR. 983-002-011:
				PR. 983-002-012:
				PR. 983-002-017:
				PR. 983-002-018:
				PR. 983-002-019:
				PR. 983-016-006:
				PR. 983-016-010
				PR. 983-016-011
				PR. 983-016-013
				PR. 983-016-015:
				PR. 983-016-017:
				PR. 983-016-019:
				PR. 983-016-021:
				PR. 983-016-023:
				PR. 983-016-030:
				PR. 983-016-036:
				PR. 983-016-041:
B04135	10	Mon, Nov 05, 1990		Protocol Amendment (New Investigators)
				PR. 983-002-004:
				PR. 983-002-005:
				PR. 983-002-007:
				PR. 983-002-015:
				PR. 983-002-016:
				PR. 983-002-020:
				PR. 983-016-003:
				PR. 983-0016-012:
				PR. 983-016-014:
				PR. 983-016-022:
				PR. 983-016-024:
				PR. 983-016-035:

CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04135	11	Tue, Nov 13, 1990	Protocol Amendment (New Investigators/Change in Protocol)	
			PR. 983-003-002: PR. 983-003-006: PR. 983-003-007: PR. 983-03-012: PR. 983-003-0013: PR. 983-003-014: PR. 983-003-015: PR. 983-002-027: PR. 983-016-002: PR. 983-016-004: PR. 983-016-025: PR. 983-016-027: PR. 983-016-038: PR. 983-016-040 Amendment #1: PR. 983-002-001:Changes to section 6.2 (dosage regimen) and 12 (publications of research findings). This amendment applies to all active centers in this multicenter study. Amendment #2: Pr. 983-002-027: Adds section 4.3 (criteria for exclusion of patients) to protocol. This amendment applies to the Canadian centers 983-002-024, 983-002-025, 983-002-026, 983-002-027 and 983-002-028 only.	
B04136	12	Wed, Nov 21, 1990	Protocol Amendment (New Investigators)	
			PR. 983-002-014: PR. 983-002-024: PR. 983-002-028: PR. 983-016-009: PR. 983-016-026: PR. 983-016-037: PR. 983-003-003: PR. 983-003-005: PR. 983-003-009: PR. 983-003-016: PR. 983-003-017:	
B04136	13	Wed, Nov 28, 1990	Protocol Amendment (New Investigators)	
			PR. 983-012-026: PR. 983-016-016: PR. 983-016-029:	
B04136	14	Tue, Dec 11, 1990	Minutes of FDA Meeting	
			Date: 27-Nov-90 RE: FDA Meeting to discuss the development of the cephalosporin CI-983	

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04136	15	Tue, Dec 11, 1990	Protocol Amendment (New Investigators/Change in Protocol)	
			PR. 983-002-023: PR. 983-016-032: PR. 983-016-034: PR. 983-016-042: PR. 983-003-011: Amendment #1: Pr. 983-003-016: PR. 983-003-017: 29-Oct-90: Eliminates males from the study population and increases the minimum age from 13 to 18. PR. 983-002-009: [redacted]	
B04136	16	Tue, Dec 18, 1990	Protocol Amendment (New Investigators)	
			PR. 983-016-033:	
B04136	17	Mon, Dec 31, 1990	IB Update	
			Reference 9 (1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title. Reference 28 - A[redacted]	
B04136	18	Fri, Jan 04, 1991	Protocol Amendment (New Investigators)	
			PR. 983-002-013: PR. 983-016-025: [redacted]	
B04136	19	Fri, Jan 11, 1991	Protocol Amendment (New Investigators)	
			PR. 983-016-044:	
B04136	20	Fri, Jan 18, 1991	Protocol Amendment (New Investigators)	
			PR. 983-003-018: PR. 983-002-006: [redacted]	
B04136	21	Fri, Jan 25, 1991	Protocol Amendment (New Investigators)	
			PR. 983-003-019: PR. 983-003-020: PR. 983-016-017: [redacted]	

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B04136	22	Fri, Feb 01, 1991	Protocol Amendment (New Investigators) PR. 983-002-021: PR. 983-016-031:
B04136	23	Mon, Feb 04, 1991 M. Lumpkin, MD	Letter RE: Response to FDA Request for Information RE: Dr. Sherman requested copies of the case report forms for the three clinical studies in progress, included in this submission.
B04136	24	Fri, Feb 15, 1991	Protocol Amendment (Change in Protocol) Amendment #3 983-002: Changes are in italicized print in the attached copy of the amendment. Amendment #1: 983-016: Changes two sections which are underlined in the attached amendment.
B04136	25	Thu, Feb 28, 1991	Protocol Amendment (New Investigators) PR. 983-003-008:
B04136	26	Thu, Mar 07, 1991	Protocol Amendment (New Investigators) PR. 983-017-000:
B04136	27	Fri, Mar 15, 1991	Protocol Amendment (New Investigators) PR. 983-003-021: PR. 983-002-006: [redacted] PR. 983-016-009: [redacted]
B04136	28	Tue, Mar 26, 1991	Protocol Amendment (New Investigators) PR. 983-022-000:
B04136	29	Mon, Apr 01, 1991	Information Amendment (Clinical) (1) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04136	30	Tue, Apr 02, 1991	Safety Report Patient #001 (BLP) PR. 983-016-015 AE: Pseudomembranous colitis; laboratory tests confirmed C. difficile. AE #:001-0983-91002-00

IND/NDA/DMF#:	34,738 IND	Doc Type:	FDA CORRESPONDENCE
		SubType:	IND
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B04137 31	Thu, Apr 11, 1991	Protocol Amendment (Change in Protocol) & Information Amendment (Pharm/Tox)
		Amendment #1: PR. 983-021-000: 07-Mar-91: Each subject will receive 400 MG of each CI-983 preparation. This amendment is effective on approval by the Community Researach Clinic Institutional Review Board. An abbreviated information amendment that describes the suspension follows the protocol and amendment. An abbreviated amendment describing the Parke-Davis capsule was submitted to the IND on March 26 (SN #028), and detailed information in the Fujisawa capsule was submitted in the original IND. Detailed amendments on the Parke-Davis capsule and suspension are in preparation for submission in the near future. (4) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.
B04138 32	Thu, Apr 18, 1991	Protocol Amendment (New Investigators & Change in Protocol)
		PR. 983-003-023: PR. 983-002-009: [redacted] Amendment #2: PR. 983-016-003:PR.983-016-007:PR. 983-016-017:PR. 983-016-022:PR. 983-016-024: PR. 983-016-025: PR. 983-016-037: PR. 983-016-038:01-Mar-91: Amendment increases enrollment at each study center to a maximum of 40 patients. Amendment #3: PR. 983-016-007: PR. 983-016-024: PR. 983-016-037: 14-Mar-91: Provides for collection of blood and urine samples for assessment of pharmacokinetic parameters. Amendment #4: PR. 983-002-007: PR. 983-002-010: PR. 983-002-018: 29-Jan-91: Raises the enrollment at each study center from 40 to 80 evaluable patients. Amendment #5: Pr. 983-002-018: 25-Mar-91: Raises enrollment from 80 to 125 evaluable patients.
B04138 33	Thu, Apr 18, 1991 M. Lumpkin, MD	Information Amendment (CMC)
		RE: Attached is an information amendment (RR-Reg 730-01623 and Reg 956-00111) to our IND 34,738, updating the Chemistry, Manufacturing and Controls for CI-983 100 MG and 200 MG capsules. Revised specifications and test methods for the drug substance are described in RR-Reg 730-01623. Validation of the new HPLC method for the determination of the drug substance purity is also included in the report. The drug product was previously obtained from Fujisawa Pharmaceutical Company. Research RR-Reg 956-00111 discusses the manufacturing, control and packaging of [redacted] The composition of the Parke-Davis product is identical to that of Fujisawa. The report includes a description of the manufacturing process, specification and testing methods and packaging (Continued - see central file copy)

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B04138	34	Thu, Apr 25, 1991	PR. 983-003-004: PR. 983-003-010: PR. 983-003-026: PR. 983-003-027: PR. 983-016-041: [redacted] PR. 983-016-030: [redacted]	Protocol Amendment (New Investigators)
B04139	35	Thu, Apr 25, 1991	(5) Research Reports submitted. Refer to Research Report list for RR #, date, author and title.	Information Amendment (Pharmacology/Toxicology)
B04141	36	Thu, Apr 25, 1991	Please refer to our IND safety report of 04-02-91 (SN #030), in which a case of pseudomembranous colitis was reported. A revised reporting form for this adverse event (AE #001-0983-91002-00) is being submitted at this time. The only item being changed is 12D., in which "action taken" has been revised from "discontinued" to "none". This reflects the fact that, while CI-983 was discontinued in response to abdominal cramping and diarrhea, it was not discontinued in response to pseudomembranous colitis per se, since the patient had been switched to ciprofloxacin two days before laboratory confirmation of C. difficile. If there are further questions, please call, etc.. .	Follow-Up to Safety Report
B04141	37	Thu, May 02, 1991	Amendment #1: PR. 983-022-000: 01-Apr-91: The exclusion criterion for serum ferritin levels during screening has been changed from "outside the range of 60 to 200 NG/ML or which differ by more than 15 NG/ML on repeat assay" to "outside the range of 40 to 200 NG/ML or which differ by more than 20% on repeat assay." The former criterion was too stringent; the modified range will exclude people with iron deficiency. Also, the subject population has been expanded from healthy males only to include women who have had a hysterectomy more than one year previously, and who fulfill all other criteria for the study.	Protocol Amendment (Change in Protocol)
B04141	38	Thu, May 02, 1991	PR. 983-003-022: PR. 983-002-012: See attachment of list of 23 new MD's	Protocol Amendment (New Investigators)
B04141	39	Fri, May 10, 1991	PR. 983-003-024: PR. 983-003-025: PR. 983-003-029: PR. 983-003-031:	Protocol Amendment (New Investigators)

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B04141	40	Fri, May 17, 1991 M. Lumpkin, MD S. Brennan, Ph.D.	RE: Attached is an information amendment (Research Report #'s RAR910458 and RAR 901096) to our IND 34,738, updating the Chemistry, Manufacturing and Controls for CI-983 200 MG capsules manufactured by Fujisawa Pharmaceutical Co., Ltd. on 22-Mar-91, Dr. Linda Sherman (FDA). In a telephone conversation with Dr. D. Scott (P-D), requested batch analysis, stability data and method validation data on the 200 MG capsules (lot 202601K). The method validation for the 200 MG capsules, according to Fujisawa, is the same as that included in the Appendix 14 (RAR900020), Volume 2 of the original IND submission. (Continued- see central file copy)	Information Amendment (CMC)
B04141	41	Fri, May 24, 1991	PR. 983-003-030: PR. 983-016-023: [redacted] Addendum #2: PR. 983-016-042: 23-Apr-91: Addendum adds a section on pharmacokinetic measurements in spatum and plasma as an option. Addendum #3: 983-016-042: 23-Apr-91: Addendum adds a section on post-therapy visits to determine relapse. These addenda are for this site only.	Protocol Amendment (New Investigators/Change in Protocol)
B04141		Tue, May 28, 1991 D. Scott M. Lumpkin	RE: Reference is made to your investigational new drug application (IND) submitted May 2, 1990, pursuant to section 507 of the Federal Food Drug and Cosmetic Act for use of CI-983 ("Cefdinir") capsules. We have completed our review of your May 2, 1990, submission and have the following recommendations with respect to the phase I study as well as any future studies. The following comments are specific with respect to the phase I study. (Continued - see central file copy)	FDA Letter RE: FDA Recommendations
B04141		Tue, May 28, 1991 S. Scott M. Lumpkin	RE: Reference is made to your investigational new drug application (IND) submitted May 2, 1990, pursuant to section 507 of the Federal Food, Drug and Cosmetic Act for the use of CI-983 capsules. We also reference your submission of protocols (IND 34,738, SN #005) dated September 24, 1990, for the treatment of uncomplicated urinary tract infections and for the treatment of lower respiratory tract infections. This letter refers to our meeting on Nov. 27, 1990 and related telephone conversation between members of your staff and Dr. Linda Sherman on Oct. 8, 1990, Feb. 20, 1991, and most recently, Mar. 13, 1991. (Continued - see central file copy)	FDA Letter RE: IND Submissions
B04141	42	Fri, Jun 14, 1991	PR. 983-003-028:	Protocol Amendment (New Investigators)

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B04141	43	Tue, Jun 18, 1991 M. Lumpkin, MD H. Holden	Letter RE: Protocol Amendment (New Protocol) RE: Please refer to IND 34,738 for our cephalosporin CI-983 under clinical investigation, and to our meeting held with members of your division on Nov. 27, 1990. At that meeting, a pediatric pharmacokinetic study was discussed that was to be conducted prior to pediatric efficacy trials. We also agreed that we would send a draft protocol for review before planning to initiate the study. This protocol is included in this submission, and desk copies are included for Dr. Linda Sherman and Dr. See Lam. This will be a single dose study of two concentrations of drug, 4 MG/KG and 8MG/KG; each concentration will be studies in 12 children. We have identified investigational sites which will be able to recruit both pediatric patients being treated for an infection. (Continued - see central file copy)
B04141	44	Tue, Jun 18, 1991	Protocol Amendment (New Investigators) PR. 983-002-030:
B04141	45	Tue, Jun 25, 1991 M. Lumpkin, MD D. Scott, Ph.D.	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-003-022: RE: On 01-Apr-91 (SN #029), we submitted a research report RR-Memo 724-00134. Research report number RR-Memo 724-00134 was inadvertently used twice therefore, we are requesting that you note the change of research report number to RR-Memo 724-00145. This report is being resubmitted at this time to correct your files. No text in the report has been changed.
B04142	46	Wed, Jul 10, 1991 M. Lumpkin D. Scott	Information Amendment (Clinical) (1) Research Report submitted. Refer to Research Report list for RR #, date, author and title. RE: This is an interim analysis of three studies of CI-983 in adults and adolescents which are being conducted under IND 34,738. This analysis is submitted in partial fulfillment of the requirements for initiation of pediatric studies with CI-983, as agreed to in our meeting of 27-Nov-90 and your letter of 28-May-91 regarding the IND. The studies evaluated are two double-blind, randomized, comparative multicenter studies of CI-983 in the treatment of uncomplicated urinary tract infections (studies 983-2 and 983-3), and one open-label, dose-finding, multicenter study in patients with lower respiratory tract infections (study 983-16). By the cutoff date of 28-Feb-91, 340 patients had entered these studies, and 272 completed treatment and the short-term follow-up visit. (Continued - see central file copy)

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B04150	47	Wed, Jul 10, 1991	Protocol Amendment (New Investigators) PR. 983-002-008: [redacted] PR. 983-002-011: [redacted] PR. 983-002-018: [redacted] PR. 983-016-031: [redacted]
B04150	48	Tue, Jul 23, 1991	Annual Report Issue Date: 22-Jul-91
B04150	49	Wed, Jul 31, 1991 M. Lumpkin D. Scott	Letter RE: Information Amendment RE: Attached for your information and files are additions to a research report entitled, "Twenty-Six-Week Oral Toxicity Study of Cefdinir in Rats" dated 14-Mar-91 (RR 745-01758 which was filed under this IND on 25-Apr-91 (SN #49). [redacted] replace pages I, 298 through 349, and insert new pages 350 through 377. These additions had no significant impact on the study results. [redacted]
B04150	50	Wed, Jul 31, 1991	Protocol Amendment (New Investigators) PR. 983-002-008: [redacted] PR. 983-016-025: [redacted]
B04150	51	Thu, Aug 15, 1991 M. Lumpkin S. Brennan	Letter RE: Response to FDA Request for Information RE: Please refer to our IND for cefdinir (CI-983), cephalosporin for oral administration. Cefdinir is being studied for its usefulness in the treatment of several types of community-acquired infections in adults and children. The data required to be submitted and reviewed prior to initiation of any pediatric work was outlined in your IND review letter of 28-May-91 (general comment 6). These items are cited below, along with the dates on which they were or are being submitted to the IND. (Continued - see central file copy)
B04150	52	Wed, Aug 21, 1991	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-016-027: [redacted] PR. 983-016-041: [redacted] Amendment #6: PR. 983-016: Increases enrollment from 20 to a maximum of 60 patients. Applies to centers 983-016-017, 983-016-024, 983-016-025, 983-016-033, 983-016-037 and 983-016-038. Amendment #2: CI-983-016: 18-Apr-91: Adding center 983-016-015 (SN #32).

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B04150	53	Wed, Aug 21, 1991		Information Amendment (Pharmacology/Toxicology)
			(1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.	
B04150	54	Wed, Aug 21, 1991 M. Lumpkin		Letter RE: Information Amendment
			RE: In an information amendment (SN #33) to our IND 34,738 for cefdinir capsules submitted to you on 18-Apr-91, we updated the Chemistry, Manufacturing and Control information for the manufacture of 100 and 200 capsules of cefdinir by Parke-Davis [redacted] Attached is an information amendment to add the 300 MG/ capsules strength. The 300 MG capsules are compositionally proportional to the lower strengths of capsules (3 time and 1.5 times the net weights of 100 and 200 MG capsules respectively) since they are filled from the same granulation. The sample preparation in the assay of the 300 MG capsules is the same as reported in the above mentioned amendment (SN #33). (Continued - see central file copy)	
		S. Brennan		
B04150	55	Wed, Aug 28, 1991 M. Lumpkin		Letter RE: Request for Meeting
			RE: We are studying the oral cephalosporin, cefdinir, under IND 34,738, and plan to initiate our major phase 3 program during the forth quarter of this year. At this time, we are requesting an end-of-phase 2 meeting, which we have discussed with Dr. Linda Sherman, the FDA Medical Reviewer, who agrees that a meeting in late October or early November would be appropriated. An outline of a proposed agenda is attached. A detailed agenda, clinical development plan, and proposed issues for discussion will be sent for your review about a month before the scheduled meeting. (Continued - see central file copy)	
		D. Scott		
B04150	56	Wed, Aug 28, 1991		Protocol Amendment (New Investigators)
			PR. 983-003-033: PR. 983-002-022: [redacted] PR. 983-016-017: [redacted] PR. 983-016-024: [redacted]	
B04150	57	Fri, Sep 13, 1991		Protocol Amendment (New Investigators & Change in Protocol)
			PR. 983-025-000: Conducted in Canada Amendment #1: PR. 983-025-000: 30-Aug-91: Specify 300 MG capsules under "Description of Medications"	

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B04151	58	Thu, Sep 19, 1991 M. Lumpkin D. Scott	RE: We are submitting a final report on CI-983 and iron hemostasis (RR 720-02973). Parke-Davis has investigated whether cefdinir has any effect on iron hemeostasis in a number of in-vitro, animal, and clinical studies. This work has demonstrated conclusively that cefdinir does not cause significant changes in any non-invasive parameter of iron homeostasis.	Letter RE: Information Amendment (Clinical)
B04153	59	Thu, Sep 19, 1991	PR. 983-002-032: PR. 983-002-033: PR. 983-002-034: PR. 983-002-035: PR. 983-002-036: PR. 983-002-037:	Protocol Amendment (New Investigators)
B04153	60	Thu, Sep 19, 1991 M. Lumpkin S. Brennan	RE: Attached is an information amendment (RR-Reg 956-00113) to our IND 34,738, updating the Chemistry, Manufacturing and Controls for cefdinir powder for oral suspension. In the IND amendment of 11-Apr-91 (SN #31), an oral suspension formulation of cefdinir was described. This formulation was used in Parke-Davis study 983-021-0 to determine its relative bioavailability to cefdinir capsules. On 13-Aug-91, the IND was amended (SN #51) to provide for a revised formulation. In the amendment, a brief description of the manufacturing and controls for the revised formulation were provided. At that time a commitment was made to provide a detailed manufacturing and controls section. (Continued - see file copy)	Letter RE: Information Amendment (CMC)
B04153	61	Wed, Sep 25, 1991 M. Lumpkin D. Scott	RE: As requested by Dr. Linda Sherman, we are outlining the protocol changes made in study 983-023-000: "A Single-Dose Safety Tolerance, and Pharmacokinetic Study of CI-983 in Pediatric Patients/Subjects", as described by telephone with Dr. Sherman, Dr. See Lam, and Mr. Carmen Debellas on 08-Aug-91 and in a brief follow-up conversation with Dr. Sherman on 09-Aug-91. Parke-Davis participants were Dr. Robert Guttendorf (Pharmacokinetics/Drug Metablism), Ms. Peggy Hawkins (Clinical Pharmacology), Dr. Drusilla Scott (Regulatory Affairs), and Dr. Artemios Vassos (Clinical Pharmacology). The items are listed below in the order they were discussed. (Continued - see file copy)	Letter RE: Response to FDA Request for Information
B04153	62	Thu, Sep 26, 1991	PR. 983-002-034:	Protocol Amendment (New Investigators)

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B04153	63	Wed, Oct 02, 1991 M. Lumpkin D. Scott	Letter RE: Review of Protocols RE: Attached are planned protocols for two adult phase 3 studies: 1) Protocol 983-004 2) Protocol 983-008 We anticipate starting these studies in early Nov-91 and would appreciate any comments you have on the drafts.
B04153	64	Thu, Oct 10, 1991 M. Lumpkin H. Holden	Letter RE: Response to FDA Request for Information RE: Per the request of Dr. Linda Sherman, enclosed are four copies of the case report forms for the following studies: 1) Protocol 983-004 2) Protocol 983-008 In addition, enclosed is one desk copy of the two protocols that were submitted on 02-Oct-91 (SN #63) corresponding to the above cited case report forms. Questions contact ———
B04153	65	Thu, Oct 10, 1991 M. Lumpkin H. Holden	Letter RE: Response to FDA Request for Information RE: Reference is made to our IND 34,738 for CI-983 capsules, to your letter of 28-May-91, to our letters to the IND of 10-Jul-91, 15-Aug-91 and 19-Sep-91, and to phone discussions with Dr. Linda Sherman of your division on 07-Oct and 08-Oct-91. As requested by Dr. Sherman, we are providing brief summaries of our previously submitted responses to the questions addressed to us on page 6 (item 6) in your letter of 28-May-91 dealing with the data requested to support clinical studies in the pediatric population. The summaries are presented as follows: (Continued - see file copy)
B04153	66	Fri, Oct 18, 1991	Protocol Amendment (Change in Protocol) Amendment #1: PR. 983-023-000: 17-Sep-91:Adding information to study population regarding inclusion criteria and exclusion criteria.
B04153	67	Thu, Oct 24, 1991	Protocol Amendment (New Investigator) PR. 983-002-031:
B04153	68	Thu, Nov 07, 1991	Information Amendment (Pharmacology/Toxicology & Clinical) (3) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04153	69	Thu, Nov 14, 1991	Protocol Amendment (New Investigators) PR. 983-002-007: [redacted] PR. 983-001-009: [redacted] (Returned from active military service and will resume responsibility of principal investigator.

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B04153	70	Wed, Nov 27, 1991 M. Lumpkin D. Scott	PR. 983-004-001: PR. 983-004-004: PR. 983-004-011: PR. 983-004-014: PR. 983-004-021: PR. 983-004-025: PR. 983-004-028: PR. 983-004-029: PR. 983-004-031: PR. 983-004-034: PR. 983-004-038: PR. 983-004-039: PR. 983-004-050: PR. 983-004-051: RE: We have discussed this protocol with Dr. Linda Sherman, the Medical Reviewer, by telephone, and have attached an information amendment regarding issues raised and our response to them immediately after this letter. The protocol is being amended as described in this list, and these amendments will be submitted when finalized. Issue 10 concerns the inclusion of clinical response in the definition of superinfection as raised by the reviewer. We have provided the rationale for our current definition, if necessary, after coming to an agrement with the agency. We also discussed a skin and skin structure protocol with Dr. Sherman (study 983-008). (Continued - see file copy)	Protocol Amendment (New Investigators) Letter RE: Protocol Amendment (Clinical)
B04153	71	Wed, Dec 04, 1991	(2) Research Report submitted. Refer to Research Report list for RR #, date, author and title.	Information Amendment (Clinical)
B04153	72	Fri, Dec 06, 1991 M. Lumpkin D. Scott	RE: We are submitting a protocol for your review, "An Investigator-Blinded, Randomized, Comparative Multicenter Study of Cefdinir (CI-983) VS Augmentin in the Treatment of Acute Otitis Media With Effusion in Pediatric Patients (Protocol 983-011)" and would appreciate any comments that you have. This study will be conducted in Europe and is planned to start in late Jan-92. Of note at this time is section 4.3.5. The protocol will be amended to exclude patients with a serum creatinine level of 1.5, rather than, 2 times the upper limit of normal. We had agreed to make this modification in two other protocols we discussed with the Medical Reviewer, Dr. Linda Sherman. At this time also, we are formally submitting a list of issues we discussed with her by phone on a skin structure protocol (983-004). These were faxed. Questions call ------	Letter RE: Information Amendment (Clinical)

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B04153	73	Thu, Dec 12, 1991		Protocol Amendments (New Investigators)
			PR. 983-004-007: PR. 983-004-013: PR. 983-004-022: PR. 983-004-023: PR. 983-004-026: PR. 983-004-037: PR. 983-004-049 PR. 983-002-033: [redacted]	
B04154	74	Thu, Dec 19, 1991		Protocol Amendments (New Investigators)
			PR. 983-004-012: PR. 983-004-030: PR. 983-004-035: PR. 983-004-036: PR. 983-004-040: PR. 983-004-045: PR. 983-004-048 PR. 983-002-019: [redacted] PR. 983-016-016: [redacted]	
B04154	75	Thu, Dec 19, 1991		Information Amendment (Clinical)
			(1) Research Report submitted. Refer to Research Report list for RR #, date, author and title.	
B04154	76	Thu, Dec 19, 1991		Letter RE: Information Amendment (Clinical)
			RE: Attached is a preliminary report on a recently completed study entitled, "A Single-Dose Safety, Tolerance, and Pharmacokinetic Study of CI-983 in Pediatric Patients/Subjects." This study protocol was submitted 19-Sep-91 (SN #58) and a minor amendment was submitted on 25-Sep-91 (SN #61). Data from this pilot study have been used to assess tolerance and pharmacokinetics of the pediatric suspension formulation in children, and to aid in selection doses for the pediatric phase 3 program. Questions contact-------	
B04154	77	Mon, Dec 30, 1991		Letter RE: General Correspondence FDA Meeting
		M. Lumpkin	RE: Attached is a copy of our letter to Ms. Sandy Childs of your division concerning the briefing package for our end-of-phase 2 meeting scheduled 13-Jan-92. Questions contact-------	
		D. Scott		
B04154	78	Thu, Jan 02, 1992		Protocol Amendment (New Investigators)
			PR. 983-003-035: PR. 983-003-036: PR. 983-003-037:	

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B04154	79	Thu, Jan 02, 1992		Information Amendment (Clinical)
				(2) Research Report submitted. Refer to Research Report list for RR #, date, author and title.
B04155	80	Thu, Jan 09, 1992		Protocol Amendment (New Investigators)
				PR. 983-008-002: PR. 983-008-003: PR. 983-008-004: PR. 983-008-005: PR. 983-008-006: PR. 983-008-007: PR. 983-008-008: PR. 983-008-009: PR. 983-008-010: PR. 983-008-011: PR. 983-008-012: PR. 983-008-014: PR. 983-008-016: PR. 983-008-017: PR. 983-008-018: We discussed this protocol with Dr. Linda Sherman, the Medical Reviewer, by telephone, on 06 and 08-Nov, and an information amendment regarding issues raised and our response to them was submitted on 06-Dec-91 (SN #72). This list is included again following (Tab 2). The amendments agreed to are being processed, and will be submitted when finalized. We also notify you of a clinical study to be conducted, in normal subjects, in accordance with the attached protocol 983-030-000 entitled "A Study to Evaluate Potential Pharmacokinetic Interactions Between Maalox and CI-983 (Cefdinir)" (Tab 3). PR. 983-008-019: PR. 983-008-021: PR. 983-008-022: PR. 983-008-024: PR. 983-008-025: PR. 983-008-028: PR. 983-008-034: PR. 983-008-036: PR. 983-008-049: PR. 983-008-052: PR. 983-004-009:

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/, Report No.
B04155	81	Fri, Jan 17, 1992		Protocol Amendments (New Investigators)
			PR. 983-004-006: PR. 983-004-033: PR. 983-004-041: PR. 983-008-015: PR. 983-008-020: PR. 983-008-035: PR. 983-008-037: PR. 983-008-040: PR. 983-008-044: PR. 983-008-045: PR. 983-008-047: PR. 983-008-050: PR. 983-002-007: [redacted] PR. 983-004-001: [redacted]	
B04155	82	Fri, Jan 24, 1992		Protocol Amendment (New Investigators)
			PR. 983-004-010: PR. 983-004-024:	
B04155	83	Fri, Jan 24, 1992		Information Amendment (Clinical)
			(2) Research Report submitted. Refer to Research Report list for RR #, date, author and title. RR 744-000444 - This report supercedes RR-Memo 724-00125 (Interim Report of Study) which was submitted on 11-Oct-90 (SN #007).	
B04155	84	Thu, Jan 30, 1992		Protocol Amendment (New Investigators)
			PR. 983-004-005:	
B04155	85	Mon, Feb 17, 1992		Protocol Amendment (New Investigators)
			PR. 983-008-013: PR. 983-008-023: PR. 983-002-010: [redacted] PR. 983-004-051: [redacted] PR. 983-008-006: [redacted] PR. 983-008-033: [redacted]	

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04155	86	Tue, Feb 18, 1992	Minutes of FDA Meeting	
			Date: 13-Jan-92 FDA meeting regarding the end-of-phase 2 for the oral cephalosporin cefdinir; the overheads presented at the meeting are included. This report was reissued due to a typographical error; this is its initial submission to the IND. Thus updated brochure supersedes RR-X 720-02821 which was submitted on 14-Sep-90 (SN #4).	
B04155	87	Tue, Feb 18, 1992	IB Update	
			Date: 24-Oct-91/07-Feb-92 RR-X 720-02983 Authors: [redacted] "Investigator's Brochure: CI-983 (Cefdinir)"	
B04155	88	Tue, Feb 25, 1992	Protocol Amendment (New Investigators)	
			PR. 983-029-000: Pr. 983-004-016: [redacted] PR. 983-004-019: [redacted]	
B04155	89	Tue, Feb 25, 1992	Letter RE: Response to FDA Request for Information	
		M. Lumpkin	RE: Dr. Barry Paull participated as principal investigator in study 983-002-011 conducted under this IND (a double-blind, randomzied comparative multicenter study of CI-983 versus trimethoprim/sulfamethoxazole in the tratment of uncomplicated urinary tract infections). In Nov-91, we received a letter from Dr. Frances Kelsey of CDER's Division of Scientific Investigations. This letter indicated that, in response to allegations of improper conduct during a clinical study with the investigational drug azelastine, Dr. Paull has agreed to no longer serve as an investigator or subinvestigator of investigational drugs. (Continued - see file copy)	
		D. Scott		
B04156	90	Fri, Mar 06, 1992	Protocol Amendment (New Investigators)	
			PR. 983-034-000: PR. 983-035-000: PR. 983-004-052: PR. 983-004-056: PR. 983-002-002: [redacted] PR. 983-008-021: [redacted]	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

Cl#: 983 | Sub Date: 4/30/90

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Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No
B04156	91	Mon, Mar 16, 1992		Letter RE: Materials for Meeting
			RE: Enclosed are briefing materials for a working meeting on cefdinir scheduled for 23-Mar. Desk copies are provided for the scheduled attendees, Drs. Sherman and Albrecht, Mr. Debellas and for Dr. Harkins, who we hope may be able to attend at least the part of the meeting on subsetting logic. Three protocols are included in this package. While we welcome any comments on the study design, we hope to discuss in detail section 8.2, date interpretation. This section is similar in all three protocols, and can be found on the designated pages: (Continued - see file copy)	
B04156	92	Mon, Apr 06, 1992		Follow-Up to Safety Report
			RE: Please refer to our IND Safety Report of 2-Apr-91 (SN #030) and the follow-up report of 25-Apr-91 (SN #036) in which a case of pseudomembranous colitis was reported. We are now submitting a second follow-up report that contains minor corrections based on a recent review. Item 12D, action taken, on the reporting form has been changed back to the original "discontinued" from "none" to reflect that cefdinir was discontinued directly in response to the symptoms of pseudomembranous colitis. The date of event onset has accordingly been corrected from 20-Mar-91 to 17-Mar-91 (items 4-6). Finally, item 12B has been updated to note that the patient recovered. The summary at the end of the form has been revised with the updated information. Questions contact———	
B04156	93	Wed, Apr 08, 1992		Safety Report
			Patient #: None (SA) PR. AE: A 17-year old female who received cefdinir (300 MG/DAY) for an upper respiratory tract infection developed nausea, and a feeling of suffocation and unconsciousness. Her pulse was 112 and blood pressure was 106/52. She was unresponsive to auditory stimuli. She was given fluid relplacement and hydrocortisone and regained consciousness the next morning. The patient has recovered.	

Cl#: 983 | Sub Date: 4/30/90
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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04156	94	Fri, Apr 10, 1992		Protocol Amendment (New Investigators & Change in Protocol)
			PR. 983-010-001: PR. 983-010-008: PR. 983-010-009: PR. 983-004-027: PR. 983-010-032: PR. 983-010-053: PR. 983-008-026: Amendment #1: PR. 983-004: 27-Nov-91: We are also sumbitting addendum A for study 983-004, which will pertain to centers 983-004-001, 983-004-002, 983-004-003, 983-004-005, 983-004-006, 983-004-007, 983-004-011, 983-004-012, 983-004-014, 983-004-015, 983-004-016, 983-004-018, 983-004-020, 983-004-025, and 983-004-034. Amendment #1: PR. 983-008: 9-Jan-92: Addendum A for study 983-008 is submitted as well and will pertain to centers 983-008-001, 983-008-002, 983-008-003, 983-008-006, 983-008-009, 983-008-010, 983-008-011, 983-008-028, 983-008-029, and 983-008-031. PR. 983-004: [redacted] PR. 983-004: [redacted]	
B04157	95	Thu, Apr 16, 1992		Protocol Amendment (New Investigators)
			PR. 983-010-002: PR. 983-010-004: PR. 983-010-011:	
B04157	96	Wed, Apr 22, 1992		Protocol Amendment (New Investigators)
			PR. 983-038-002: PR. 983-038-019: PR. 983-038-022: PR. 983-038-005: PR. 983-038-006:	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No:
B04157	97	Wed, May 13, 1992	Protocol Amendment (New Investigators) PR. 983-011-003: PR. 983-011-022: PR. 983-010-003: PR. 983-010-012: PR. 983-038-001: PR. 983-038-004: PR. 983-038-006: PR. 983-038-011: PR. 983-038-015: PR. 983-038-016: PR. 983-038-017: PR. 983-038-023: Amendment #1: PR. 983-011: 13-May-92: Amendment #1 (including the rationale) for this study is also attached. We will obtain similar amendments for all active centers of the multicenter but will not submit them in order to eliminate paperwork. (Tab 1) Amendment #2: PR. 983-004: 27-Nov-91: We are attaching amendment #2 (including the rationale) for this study. We will obtain similar amendments for all active centers of the multicenter but will not submit them in order to eliminate paperwork. (Tab 2) PR. 983-004-031: [redacted] PR. 983-004-001: 29 subinvestigators have been added to work during the conduct of study 983-004-001. (See file copy for list of names) (Tab 3)
B04157	98	Tue, May 19, 1992 M. Lumpkin D. Scott	Letter RE: Protocol Amendment (New Protocol) RE: Attached are two protocols for your review, protocol 983-013 entitled, "Cefdinir Versus Cephalexin in the Treatment of Acute Uncomplicated Skin and Skin Structure Infections in Pediatric Patients," and Protocol 983-036, entitled, "An Investigator-Blinded, Randomized Comparative, Multicenter Study of Cefdinir Versus Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients." Study 983-013 is similar in design to the adult SSSI study, protocol 983-008, entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of CI-983 Versus Cephalexin in the Treatment of Skin and Skin Structure Infections," submitted on 9-Jan-92, (SN #094), although the follow-up visits are at later time points. Questions contact-------

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04157	99	Fri, May 22, 1992		Protocol Amendments (New Investigators & Change in Protocol)

PR. 983-006-001:
PR. 983-006-002:
PR. 983-006-005:
PR. 983-006-010:
PR. 983-006-011:
PR. 983-006-012:
PR. 983-006-013:
PR. 983-006-014:
PR. 983-006-016:
PR. 983-006-017:
PR. 983-006-018:
PR. 983-006-021:
PR. 983-006-024:
PR. 983-006-025:
PR. 983-006-026:
PR. 983-006-027:
PR. 983-006-028:
PR. 983-006-030:
PR. 983-006-033:
PR. 983-006-034:
PR. 983-006-038:
PR. 983-011-002:
PR. 983-011-008:
PR. 983-011-009:
PR. 983-011-013:
PR. 983-011-014:
PR. 983-011-026:
PR. 983-011-028:
PR. 983-038-018:
Addendum B: 13-May-92: PR. 983-011: Addendum B for only the [redacted] centers 983-011-026 and 983-011-028 is attached.
This addendum specifies that tympanocetesis will not be allowed in any [redacted] site participating in the 983-011 study, in accordance with the recommendation of the Ethical Review Committee. This addendum allows a change to the specified age range of the patient population recruited into 983-011 study to give a minimum age of 12 months. Also the first 3 patients to be recruited must be aged 6 or over.
This addendum specifies a maximum amount of blood 5 ML, to be sampled at any one visit for the purpose of haematologial and biochemical analysis.

SubType: IND

Cl#: 983 | Sub Date: 4/30/90

Generic:

Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No: Contents/Report No/
B04157	100	Fri, May 22, 1992	Letter RE: Protocol Amendment (New Protocol)
			RE: Attached are two protocols for your review, protocol 983-026 entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir VS. Amoxicillin/Clavulanic Acid in the Treatment of Community-Acquired Bacterial Pneumonia" and protocol 983-037 entitled, "A Double-Blind Randomized, Comparative, Multicenter Study of Cefdinir (Cl-983) VS. Amoxicillin with Clavulanic Acid in the Treatment of Acute Bacterial Maxillary Sinusitis (prtocol 983-037)." These studies in adults/adolescents will be conducted outside North America, but are similar in design to the North American studies currently in progress under this IND, (protocol 983-004, pneumonia - submitted 27-Nov-91,. . . . . (Continued - see file copy)
B04157	101	Tue, Jun 02, 1992	Letter RE: Response to Request for Information
		M. Lumpkin	RE: Recently we sent four protocols to the IND for review, SN #098 on 19-May-92 and SN #100 on 22-May 92. Dr. Sherman called to ask if case report forms for the protocols were available. Draft case report forms for the pediatric SSSI study (983-013) are availalbe at this time and are included in this submission. The other studies are starting later, and drafts of the case report forms are not yet available. Questions contact ------
		D. Scott	

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04157	102	Thu, Jun 11, 1992		Protocol Amendment (New Investigators & Change in Protocol)

PR. 983-006-003:
PR. 983-006-007:
PR. 983-006-008:
PR. 983-006-009:
PR. 983-006-019:
PR. 983-006-020:
PR. 983-006-029:
PR. 983-006-035:
PR. 983-006-039:
PR. 983-006-040:
PR. 983-011-004:
PR. 983-011-032:
PR. 983-038-009:
PR. 983-038-010:
PR. 983-038-020:
Amendment #2: PR. 983-003: 13-Nov-90: We have obtained similar amendments for all active centers of the mullticenter but did not submit to eliminate paperwork.
PR. 983-006-024: [redacted]
PR. 983-002-017: [redacted]
PR. 983-004-014: [redacted]
PR. 983-004-015: [redacted]
PR. 983-004-040: [redacted]
PR. 983-004-012: [redacted]
PR. 983-004-017: [redacted]
PR. 983-008-019: [redacted]
PR. 983-008-028: [redacted]
[redacted]
PR. 983-008-032: [redacted]

B04158	103	Thu, Jun 18, 1992		Protocol Amendment (New Investigators)

PR. 983-011-012:
PR. 983-011-019:
PR. 983-011-020:
PR. 983-011-021:

B04158	104	Tue, Jun 23, 1992		Safety Report

Patient #: None (YO)
PR #: None
AE: A 77-year old male who developed allergic vasculitis while on cefdinir therapy for the treatment of bronchitis. This event has been reported from Japan and did not occur in a study being conducted under the IND. The reporting physician considered the allergic vasculitis possibly related to study drug, and that the event prolonged hospitalizaiton.
This event is considered unexpected; no prior cases of allergic vasculitis have been reported to the Waers database for cefdinir.
AE: #081-0983-920006-00

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

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Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04158	105	Thu, Jun 25, 1992	Safety Report
			Patient: #12 (RHS) PR. 983-008-001 AE: A 22-year old male was hospitalized for bloody diarrhea which the investigator assessed as probably related to cefdinir and for appendicitis which was regarded as possibly related to cefdinir. There have been no previous reports of bloody diarrhea or of appendicitis to the Parke-Davis Safety Database. AE: #0001-0983-920008-00
B04158	106	Thu, Jun 25, 1992	Protocol Amendment (New Investigator & Change in Protocol)
			PR. 983-006-023: PR. 983-006-036: PR. 983-011-024: PR. 983-011-025: PR. 983-011-033: PR. 983-011-034: PR. 983-011-035: Addendum B: PR. 983-011: 22-May-92: Addendum B applies to all [redacted] centers.
B04158	107	Thu, Jun 25, 1992	Protocol Amendment (New Investigator)
			PR. 983-013-008: PR. 983-013-011: PR. 983-013-016:
B04158	108	Fri, Jun 26, 1992	Letter RE: Protocols for Review
		M. Lumpkin	RE: Attached are two protocols for your review, protocol 983-007 entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Group A B-Hemolytic Streptococcal Pharyngitis/Tonsilitis Infections" and protocol 983-005 entitled, "A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) VS Cefuroxime Axetil in the Treatment of Acute Exacerbations of Chronic Bronchitis (protocol 983-005)." Study 983-007 is a North American study in adult/adolescents that is similar in design to the international pediatric protocol, study 983-036 (sent for review on 19-May-92, SN #098). Questions contact--------
		D. Scott	
B04158	109	Tue, Jul 07, 1992	Protocol Amendment (New Investigators)
			PR. 983-011-007: PR. 983-011-010: PR. 983-011-017: PR. 983-011-023:

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No/	Report Title/ Report No
B04158	110	Thu, Jul 16, 1992		Protocol Amendment (New Investigators)

PR. 983-031-000:
PR. 983-040-000:
PR. 983-041-000:
PR. 983-006-006:
PR. 983-011-001:
PR. 983-011-005:
PR. 983-013-001:
PR. 983-013-005:
PR. 983-013-006:
PR. 983-013-009:
PR. 983-013-012:
PR. 983-013-013:
PR. 983-013-014:
PR. 983-013-017:
PR. 983-013-018:
PR. 983-013-020:
PR. 983-004-041: [redacted]
PR. 983-004-002: [redacted]
PR. 983-008-001: [redacted]
PR. 983-008-024: [redacted]

B04158		Thu, Jul 23, 1992		Letter from FDA: RE: [redacted]

In a letter dated 20-Nov-92, I asked that you inform me of your intentions with regards to data verification of the studies conducted by [redacted] A copy of the letter is enclosed. As of this date, I have received no reply.
Please let me know of your intentions either to [redacted]

F. Kelsey, Ph.D., M

B04158	111	Fri, Aug 07, 1992		Protocol Amendment (New Investigator & Change in Protocol)

M. Lumpkin

On 22-May-92 (SN #99), we notified you of a clinical multicenter study to be conducted in accordance with protocol 983-006 entitled, "An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (600 MG QD and 300 MG BID) Versus Augmentin (500 MG TID) in the Treatment of Acute Maxillary Sinusitis for 10 Days." We are adding centers 983-006-022 and 983-006-032 to the multicenter study.
Also, on 10-Apr-92 (SN #92), we notified you of a clinical multicenter study to be conducted in accordance with protocol 832-010 entitled, "An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Augmentin in the Treatment of Acute Suppurative Otitis Media With Effusion in Pediatric Patients." We are adding center 10 to this multicenter study. (Continued - see file copy)

D. Scott

B04159	112	Fri, Aug 07, 1992		Annual Report

M. Lumpkin

Attached for you information and files is the annual report dated 7-Aug-92, for our cefdinir capsules and suspension IND 34,738.

D. Scott

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No.	Report Title/ Report No.
B04159		Thu, Aug 13, 1992 F. Kelsey R. Spivey	Letter RE: [redacted] As we discussed on the telephone (11-Aug-92), I am re-submitting our response to your letter of 19-Nov-91 concerning handling of data from studies conducted by [redacted] Contact-------	
B04159	113	Mon, Aug 17, 1992	PR. 983-006-004: [redacted] PR. 983-010-007: [redacted] PR. 983-013-007: [redacted] PR. 983-038-003: [redacted] Addendum B for PR. 983-010 Center 4 (Continued - see file copy)	Protocol Amendment (New Investigators & Change in Protocol)
B04159	114	Tue, Aug 18, 1992	Attached are additional draft case report forms (CRFs) for use in OUE discussion of Cefdinir protocols with Dr. L. Sherman and C. Debellas on 2-Sep-92 (1:00 pm, Room 12-21B). The protocols submitted for review are listed below. (Continued - see file copy)	Review of Protocols
B04159	115	Tue, Aug 25, 1992	PR. 983-013-003: [redacted] Additional subinvestigators (Continued - see file copy)	Protocol Amendment (New Investigators & Change in Protocol)
B04159	116	Tue, Sep 01, 1992	For your information, we are submitting a report of diarrhea with overdosage recently observed in one of the cefdinir otitis media studies (983-011) a nine-year old female developed diarrhea after receiving three times the prescribed dose of cefdinir on four separate occasions. Diarrhea is an expected event with cefdinir, and did not result in hospitalization. Although the event was reported as an overdose, it is not clear that three times is the correct dose constitutes a true overdose for a cephalosporin-type agent. We are, however, submitting the attached event data for your information. Contact--------	Information Amendment (Clinical)
B04159	117	Wed, Sep 02, 1992 M. Lumpkin D. Scott	We have been notified of the addition of several subinvestigators to several study centers. (Continued - see file copy)	Protocol Amendment (New Investigators)
B04159	118	Mon, Sep 14, 1992	PR. 983-038-007: [redacted]	Protocol Amendment (New Investigators)

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
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CI#: 983 | Sub Date: 4/30/90
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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B04159	119	Tue, Sep 22, 1992	Protocol Amendment (New Investigators & Change in Protocol) PR. 983-007-006: [redacted] PR. 983-007-009: [redacted] PR. 983-007-011: [redacted] PR. 983-007-022: [redacted] PR. 983-007-025: [redacted] Addendum A for PR. 983-007: Provides for pharmacokinetic sampling and analysis at selected sites. Contact———
B04159	120	Wed, Sep 30, 1992	Protocol Amendment (New Investigators) PR. 983-038-024: [redacted]
B04159	121	Mon, Oct 05, 1992	Protocol Amendment (New Investigators) PR. 983-007-003: [redacted] PR. 983-007-005: [redacted] PR. 983-007-014: [redacted] PR. 983-007-017: [redacted] PR. 983-007-023: [redacted]
B04159	122	Fri, Oct 09, 1992	IND Safety Report: Initial Written Report We are submitting IND safety reports on two events that were reported to us from Japan; neither event occurred in a study being conducted under the IND. Event number 14974 is an 18-year old male who reported blood diarrhea and melena. Event number 15090 is a case of a 25-year old male who had a clonoscopy and was diagnosed with hemorrhagic colitis; he was also taking diclofenac. The physician believed the event was probably related to the use of cefdinir and diclofenac (possible interaction). Both patients have recovered. No similar events have been previously reported to our worldwide adverse event reporting system. Contact———

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04159	123	Mon, Oct 19, 1992		Protocol Amendments (New Protocol/New Investigators/Change in Protocol)

PR. 983-005-005: [redacted]
PR. 983-005-006: [redacted]
PR. 983-005-007: [redacted]
PR. 983-005-008: [redacted]
PR. 983-005-009: [redacted]
PR. 983-005-010: [redacted]
PR. 983-005-017: [redacted]
PR. 983-005-019: [redacted]
PR. 983-005-020: [redacted]
PR. 983-004-058: [redacted]
PR. 983-007-002: [redacted]
PR. 983-007-016: [redacted]
PR. 983-007-0021: [redacted]
PR. 983-011-036: [redacted]
Addendum A for PR. 983-007-002, 983-007-013, 983-007-016, 983-007-017, 983-007-023, and 983-007-025
Addendum B for PR. 983-008-005, 983-008-006, 983-008-010, 983-008-011, 983-008-015, 983-008-019, 983-008-021, 983-008-023, 983-008-024, and 983-008-052.
PR. 983-004-001: [redacted]
(Continued - see file copy)

Barcode	Ser/ Ref#	Date	Report Title/ Report No.
B04159	124	Mon, Oct 19, 1992	IND Safety Report: Initial Written/Follow-Up Report

We are submitting an IND safety report on an event reported to us from Japan; it did not occur in a study being conducted under the IND.
This event, #15611, is a case of a 52-year old female who was hospitalized with the diagnosis of drug-induced pneumonia and nephropathy. The lymphocyte stimulation test was positive for the study medication and for the concomitant medications ibuprofen and streptokinase/streptodornae. The patient has recovered. Nephropathy has not been reported previously to our worldwide adverse event reporting system. A listing of two reported pnemonias is attached.
We are also submitting follow-up information on a previously reported event (event 13368, submitted 25-Jun-92, SN #105). The events described therein were bloody diarrhea and appendicitis. Further information regarding the bloody diarrhea had led to A modification of the classification from bloody (Continued - see file copy)

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04160	125	Wed, Oct 21, 1992 M. Lumpkin	Protocol Amendment (New Protocol & New Investigators)	New Protocol 983-026, New Center 983-026-009: P.J. Arens, MD PR. 983-026-012: [redacted] PR. 983-026-013: [redacted] PR. 983-026-014: [redacted] PR. 983-026-015: [redacted] PR. 983-026-016: [redacted] PR. 983-026-019: [redacted] PR. 983-007-001: [redacted] PR. 983-007-004: [redacted] PR. 983-007-007: [redacted] PR. 983-007-010: [redacted] PR. 983-007-020: [redacted] PR. 983-006-015: [redacted] Contact------- D. Scott
B04160	126	Wed, Oct 28, 1992	Protocol Amendment (New Investigators)	PR. 983-007-012: [redacted] PR. 983-007-019: [redacted] PR. 983-007-024: [redacted]
B04160	127	Thu, Nov 05, 1992	Protocol Amendment (New Investigators)	PR. 983-005-011: [redacted] PR. 983-005-014: [redacted] PR. 983-026-010: [redacted] PR. 983-038-012: [redacted]
B04160	128	Mon, Nov 09, 1992	Information Amendment (Pharmacology/Toxicology & Clinical)	(6) Research Report submitted. Refer to Research Report list for RR #, date, author and title. Revisions for RR 745-01572 and 745-01573. (Continued - see file copy)
B04160	129	Thu, Nov 12, 1992 M. Lumpkin	Protocol Amendment (New Protocol & Change in Protocol)	New Protocol 983-036 entitled, An Investigator-Blinded, Randomized, Comparative, Multicentre Study of Cefdinir Versus Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Paediatric Patients. New Center 983-036-003: E. [redacted] Addendum A for center 3: Increases the minimum age of entry to 12 months. Also, the first three patients to be recruited must be age 6 or over. The addendum also specifies a maximum amount of blood, 5ML, to be sampled at any one visit for hematological and biochemical analysis. Contact------- D. Scott

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B04160	130	Thu, Nov 19, 1992		Protocol Amendment (New Protocol/New Investigator/Change in Protocol)
			PR. 983-037-001: [redacted] PR. 983-037-003: [redacted] PR. 983-037-004: [redacted] PR. 983-037-005: [redacted] PR. 983-037-006: [redacted] PR. 983-037-010: [redacted] PR. 983-037-011: [redacted] PR. 983-037-012: [redacted] PR. 983-037-013: [redacted] PR. 983-037-014: [redacted] Addendum A for center 1: Increases the minimum age of entry to 18 at all 983-037 investigational sites in Finland. This addendum is in accordance with local country requirements for the clinical investigation of new drugs and changes section 4.2.2.(page 8). (Continued - see file copy)	
B04161	131	Tue, Nov 24, 1992		Protocol Amendment (New Investigator)
			PR. 983-019-001: [redacted] PR. 983-011-031: [redacted] PR. 983-007-015: [redacted] PR. 983-036-008: [redacted]	

SubType: IND

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B04161	132 Thu, Dec 03, 1992	Protocol Amendment (New Investigators & Change in Protocol)
		PR. 983-004-060: [redacted] PR. 983-004-025: New IRB address: Old Address: Institutional Review Board, VAMC, 4801 Linwood Blvd., Kansas City, MO 64128 New Address: [redacted] PR. 983-005-001: [redacted] PR. 983-005-002: [redacted] PR. 983-005-003: [redacted] PR. 983-005-004: [redacted] PR. 983-036-002: [redacted] PR. 983-036-007: [redacted] PR. 983-036-009: [redacted] PR. 983-036-016: [redacted] PR. 983-037-002: [redacted] PR. 983-037-015: [redacted] PR. 983-019-002: [redacted] PR. 983-004-016: [redacted]: Center submitted on 27-Nov-91 (SN # 0) PR. 983-038-011: [redacted] Center submitted on 13-May-92 (SN #97) PR. 983-013-005: [redacted] PR. 983-013-006: [redacted] submitted on 16-Jul-92 (SN #110) PR. 983-010-006: [redacted] submitted on 22-Apr-92 (SN #96) PR. 983-008-006: [redacted] PR. 983-008-052: [redacted] Centers submitted on 9-Jan-92 (SN #80) PR. 983-006-010: [redacted] PR. 983-006-018: [redacted] PR. 983-006-030: [redacted] Centers submitted on 22-May-92 (SN #99)
B04161	133 Tue, Dec 15, 1992 M. Lumpkin	IND Safety Report: Initial Written We are submitting a safety report on a case of hepatic dysfunction and jaundice reported from post-marketing surveillance in Japan; the event did not occur in a study being conducted under the IND. Cefdinir was begun prophylactically after an appendectomy in a 28-year-old male whose liver enzymes were elevated prior to receiving drug. Cefdinir was continued for eight days; liver enzymes peaked 7-8 weeks after therapy. There was a positive cefdiinir lymphocyte stimulation test. The reporting physician considered a possible causal relationship between the event and the drug. The PD medical reviewer considered the relationship unlikely based upon the elevation pattern and experience with other beta lactum agents. All investigators are being notified of this event. . . (Continued - see file copy)
	D. Scott	

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04161	134	Wed, Dec 16, 1992		Protocol Amendment (New Investigator)
			PR. 983-042-000:	
B04161	135	Tue, Dec 22, 1992		Protocol Amendments (New Investigators & Change in Protocol)
			PR. 983-011-016: PR. 983-006-041: Addendum A: PR. 983-006-013: PR. 983-006-026:PR. 983-006-033: 26-Mar-92: Provides for the collection of a 4-hour post-morning dose sample of blood for further pharmacokinetic analysis. PR. 983-005-013: PR. 983-026-002: PR. 983-026-003: PR. 983-026-018: PR. 983-037-007: PR. 983-037-009: PR. 983-019-004: PR. 983-004-064: PR. 983-004-065:	
B04161	136	Fri, Jan 08, 1993		Protocol Amendments (New Investigators & Change in Protocol)
			PR. 983-036-011: PR. 983-036-014: PR. 983-036-015: PR. 983-004-001: [redacted] PR. 983-007-005: [redacted] PR. 983-038-017: [redacted] New address: Institutional Review Board - see file copy PR. 983-007-024: Dropped as subinvestigator: D. McLeod,RN	
B04161	137	Mon, Jan 11, 1993		Safety Report
			Patient: # /YW PR. 983 AE: Thrombocytopenia AE: #18365 Patient: # /AS PR. 983 AE: Facial edema and larynogopharyngael edema AE: #18788 Patient: # /MO PR. 983 AE: Phabdomyolysis AE: #19153	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B04161	138	Fri, Jan 29, 1993	PR. 983-007-022: [redacted] PR. 983-007-001: [redacted] PR. 983-010-005: [redacted] [redacted] PR. 983-006-010 [redacted] PR. 983-006-033: [redacted] (Continued - see file copy)	Protocol Amendment (New Investigators)
B04161	139	Fri, Feb 05, 1993	PR. 983-004-059: [redacted] PR. 983-004-062: [redacted] PR. 983-010-013: [redacted] PR. 983-005-023: [redacted] PR. 983-026-008: [redacted] PR. 983-026-020: [redacted] PR. 983-026-021: [redacted] PR. 983-026-022: [redacted] PR. 983-036-013 [redacted] PR. 983-036-019: [redacted] PR. 983-036-020: [redacted] We have also been notified of the addition of subinvestigators to four study centers. (Continued - see file copy)	Protocol Amendment (New Investigators & Change in Protocol)
B04161	140	Mon, Feb 08, 1993	Patient: # (KM) PR.: None AE: # None (Waers event # 20230) Possibly study drug related. AE: Idiopathic interstitial pneumonia, patient was hospitalized.	IND Safety Report/Initial Written Report
B04161	141	Wed, Feb 17, 1993	We faxed Dr. L. Sherman a proposed change in our sinusitis program for cefdinir. We will be discussing it on 17-Feb-93 at 1:00 pm, at the USP, with Dr. Sherman, Mr. Dedellas, and Dr. Ralph Harkins. We are sending a copy of the proposal now so that it may be part of our official IND file. Contact——— (see file copy)	Information Amendment (Clinical)

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B04161	142	Fri, Feb 19, 1993	Protocol Amendment (New Protocol/New Investigators/Change in Protocol) New Protocol 983-043 entitled, A Study to Determine the Effect of Time of Administration of a Therapeutic Iron Dose on Cefdinir Absorption. A. Sedman, MD/E. [redacted] PR. 983-004-063: [redacted] PR. 983-011-037: [redacted] PR. 983-007-008: [redacted] Addendum B for center 8 in study 983-007 which some rewording requested by the Health Protection Bureau in Canada. PR. 983-005-016: [redacted] PR. 983-005-022: [redacted] PR. 983-026-001: [redacted] PR. 983-036-021: [redacted] PR. 983-037-008: [redacted]
B04161	143	Mon, Feb 22, 1993	IND Safety Report: Initial Written Report Patient : # (HM) PR.: Foreign Event: #20631 [redacted] Possibly related to cefdinir The events did not occur in studies being conducted under the IND; they were reported from post-marketing experience in Japan, [redacted]
B04161	144	Fri, Feb 26, 1993	Protocol Amendments: New Investigators) Added new centers: PR. 983-004-067: PR. 983-011-018: PR. 983-006-043: PR. 983-026-023: PR. 983-036-024: PR. 983-006-011: [redacted] PR. 983-006-030: [redacted] May-92 (SN # 099) PR. 983-038-009: [redacted] Center submitted on 11-Jun-92 (SN #102) PR. 983-007-017: [redacted] Center submitted on 6-Oct-92 (SN #121) PR. 983-007-012: [redacted] ter submitted on 28-Oct-92 (SN #126) Contact——

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B04161	145	Fri, Mar 05, 1993		Protocol Amendment (New Investigators & Change in Protocol)
			PR. 983-006-046: [redacted] PR. 983-036-031: [redacted] PR. 983-037-018: [redacted] We have been notified of a change of address for Principal Investigator [redacted] (PR. 983-004-029) (27-Nov-92; SN #70). Old: Simon-Williamson Clinic, P.C., 833 Princeton Avenue, S.W., Birmingham, AL 35211. New: [redacted]	
B04161	146	Fri, Mar 05, 1993		Information Amendment (Clinical)
			(3) Research Report submitted. Refer to Research Report list for RR #, date, author and title. RR 745-01748 - Page (I) Revision - Lot Number	
B05886	147	Fri, Mar 19, 1993		Protocol Amendments (New Investigator & Change in Protocol)
			Add Centers: PR. 983-004-061: PR. 983-004-066: New Subinvestigators: [redacted] submitted on 12-Dec-91 (SN #073)	
B05886	148	Fri, Apr 02, 1993		Protocol Amendment (New Investigators)
			PR. 983-036-017: [redacted]	
B05886	149	Mon, Apr 05, 1993		Closing FDA Master File 535
		M. Lumpkin	We are in the process of discontinuing our FDA Master File 535 which was initiated on 9-Apr-63 in our FDA-MIS file, SN #5. Reference is made to our second page of standard letters for protocol amendments: new protocol, in which we state, "filed in section 5 of MF 535 for Drs. Dawkins, and Vassos." This statement appears under the heading, "Investigator Qualifications." These investigators have participated in the following studies filed under IND #34,738. (Continued - see file copy)	
		D. Scott		
B05886	150	Thu, Apr 08, 1993		Protocol Amendment (New Investigators)
			PR. 983-006-048: [redacted]	

Barcode	Ser/Ref#	Date / To: / From:	RE/Report Title/Report No./Contents/Report No./
B05886	151	Tue, Apr 27, 1993 M. Lumpkin D. Scott	Protocol Amendment (New Protocol & Change in Protocol) New Protocol 983-051 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir Versus Penicillin V-K in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients. New Centers: 983-051-002: H. [redacted] 983-051-003: [redacted] 983-051-005: [redacted] 983-051-007: [redacted] MD, 983-051-011: [redacted] Regarding Protocol 983-004: Amendment #3 which notes that patients requiring therapy with magnesium- or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before and two hours after study drug dosing. We will obtain similar amendments for all remaining active centers but will not submit them in order to eliminate paperwork. PR. 983-038: Addendum A for 983-038-016, which was created to determine sputum concentrations of cefdinir after dosing in patients with secondary bacterial infections of acute bronchitis. PR. 983-006: Amendment #1 which notes that patients requiring therapy with magnesium- or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before and two hours after study drug dosing. We . . . . paperwork. PR. 983-013: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. PR. 983-005: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. PR. 983-026: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. PR. 983-037: Amendment #1 which notes that patients requiring therapy with magnesium-or aluminum-containing antacids should be instructed to withhold antacid therapy for two hours before. . .dosing. [redacted], MD will assume Principal Investigator responsibilities, [redacted] for studies 983-004-012, 983-013-018, 983-006-026 and 983-038-016.

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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B05886	152	Wed, May 19, 1993	New Protocol 983-024 entitled, A Study of Cefdinir (CI-983) Penetration into Tonsil Tissue in Patients Undergoing Elective Tonsillectomy. PR. 983-011-023: PR. 983-011-038: PR. 983-026-031: PR. 983-037-017: PR. 983-051-001: PR. 983-051-004: PR. 983-051-008: PR. 983-051-009: PR. 983-051-010: New Sub-Investigators: PR. 983-013-015: PR. 983-013-019: PR. 983-006-022: PR. 983-007-025: PR. 983-006-041: PR. 983-004-063: PR. 983-004-067:	Protocol Amendments (New Protocol & New Investigators)
B05886	153	Wed, May 26, 1993	PR. 983-051-014: Amendment #1: PR. 983-042-000: 16-Mar-93: Amendment 1 notes a change in time of tissue and blood collection for cefdinir assay, and an addition of 4 patients.	Protocol Amendment (New Investigators & Change in Protocol)
B05886	154	Wed, Jun 09, 1993	Patient: # none (RY) PR. Japan where drug is marketed by Fujisawa AE: [redacted] sulpyrine, a sulfa drug known to be associated with TEN. Possibly related to cefdinir.	IND Safety Report: Initial Written Report
B05886	155	Tue, Jun 15, 1993	Patient: # none (OT) PR. [redacted]	Safety Report

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B05886	156	Fri, Jun 18, 1993		Protocol Amendment (New Investigators & Change in Protocol)

PR. 983-007-018: [redacted]
Amendment #1 for 983-007 which notes that cefdinir has been shown to interact with Maalox. Patients requiring therapy with magnesium- or aluminum-containing antiacid therapy for two hours before and two hours after study drug dosing. We will . . . paperwork.
Addendum B for PR. 983-007-018 which notes minor revisions requested by the Canadian Health Protection Bureau (HPB).
PR. 983-026-024: [redacted]
PR. 983-026-026: [redacted]
PR. 983-026-027: [redacted]
PR. 983-026-028: [redacted]
Addenda A, B, &C for PR. 983-026: A - Provides for exclusion of patients with acute, or history of, pseudomembraneous colitis.
(Continued - see file copy)

B05886	157	Mon, Jun 28, 1993		Information Amendment (Pharmacology/Toxicology)

(1) Research Report submitted.
Refer to Research Report list for RR #, date, author and title.

B06151	158	Wed, Jul 14, 1993	158	Information Amendment (CMC)

RR-Reg 730-01959 - Updating the Chemistry, Manufacturing and Controls for the drug substance for cefdinir capsules and suspension.
In an earlier amendment (SN #33, 18-Apr-91), we updated the IND specifications and test methods for accepting the new drug substance from the manufacturer, Fujisawa Pharmaceutical Company. These specifications were established based on the limited experience of 5 early lots.
We are updating the specifications and test method to reflect current experience with the drug substance as the development of this compound progresses further. We wish to change the purity of the drug substance from 98.0 to 102.0% to 97.0 to 102.0% and the limit for the impurities PD 138339 and PD 151833 from 0.5% each to not more than 0.6% each. The specification of 98.0 to 102.0% for drug substance purity was supported by our . . . (Continued - see file copy)

B06151	159	Mon, Jul 19, 1993		IND Safety Report: Initial Written Report

Patient: MK
PR. None - Japan where drug marketed
AE: #081-0983-930006-00
AE: [redacted]

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Barcode	Ser/Ref#	Date	RE/To:/From:	Report Title/ Report No./ Contents/Report No./
B06151	160	Mon, Jul 26, 1993		Protocol Amendment (New Investigator & Change in Protocol) PR. 983-051-015: [redacted] PR. 983-010-006: Addendum B which requires that applicable centers enroll a maximum of 30 patients without baseline tympanocentesis. Subsequently, all guardians must consent to this procedure for the patient to be entered into the study. Also several subinvestigators have been added to various studies. (Continued - see file copy)
B06151	161	Tue, Aug 03, 1993		IND Safety Report: Follow-Up Report Initial Report Submitted: 19-Jul-93 (SN #159) PT: (MK) PR. Marketed Drug in Japan AE: #081-0983-930006-01 At that time, th[redacted]of [redacted] We have now learned that three concomitant drugs, flomoxef sodium, cefaclor, and sulfamethoxazole,trimethoprim were considered suspect by the reporter. Also, the course of events is now listed as impaired bone marrow, leukopenia, thrombocytopenia, DIC, sepsis, cerebral hemmorrhage, cardiac failure, and death. (Continued - see file copy)
B06151	162	Mon, Aug 09, 1993		Annual Report Attached for your information and files is our annual report. Dated: 6-Aug-93 IND: 45,738, cedfinir (CI-983) capsules and suspension
B06151	163	Thu, Aug 12, 1993		Protocol Amendment (New Investigators) PR. 983-006-049: [redacted] PR. 983-026-035: [redacted] PR. 983-026-038: [redacted] PR. 983-026-045: [redacted] PR. 983-037-020: [redacted]
B06151	164	Tue, Aug 24, 1993		Safety Report Patient: # (IT) Pr. 983 AE: #081-0983-930008-00 AE: Thrombocytopenia, disseminated intravascular coagulation (DIC), and eruption.

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B06151	165	Wed, Aug 25, 1993 M. Lumpkin D. Scott	Meeting Request for CANADA	We are requesting a meeting to discuss our planned CANDA for cefdinir, which is scheduled for 1995. Our major goal is to provide a useful means for the medical reviewer to query and create analyses from the database. For the agenda, we suggest that we describe our planned NDA, the minimum functionality expected from our CANDA, and the features we hope to be able to provide. We would then like to hear from the Agency what aspects of CANDA's you have found most useful in reviewing NDA's. We plan to bring six attendees, if possible, from the areas of Regulatory Affairs, Clinical Research, Biometrics, and Research Information Systems. We would hope that from the FDA at least the following could attend: [redacted] Good meeting days for us would be October 4, 5, 7, 8, or 11. We will provide a briefing package two weeks before the meeting.
B06151	166	Thu, Aug 26, 1993 M. Lumpkin D. Scott	Protocol Amendment: New Protocol	New Protocol: 983-048-000 entitled, A Pharmacokinetic Study of Cefdinir Concentrations in Ear Fluid and Plasma After Oral Administration of 7 mg/kg BID or 14 mg/kg QD to Pediatric Patients with Acute Suppurative Otitis Media Princ. Invest: [redacted]
B06151	167	Mon, Sep 13, 1993 M. Lumpkin D. Scott	Protocol Amendment: New Invest/Change in Protocol	New Invest: 983-026-032, 983-026-036, 983-026-037, 983-026-039, 983-026-048, 983-026-049 Princ: Invest: [redacted] Coinvest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest [redacted] Princ. Invest: [redacted] 983-026: Amendment 2 New Invest: 983-005-024 Princ. Invest. [redacted] 983-005: Addendum B, C. D

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B06151	168	Thu, Sep 16, 1993 M. Lumpkin D. Scott	Information Amendment: Clinical	We are submitting an information amendment on a case [redacted] (Adverse Event No. 081-0983-930015-00). The event did not occur in a study being conducted under the IND; it was reported from post-marketing experience by [redacted]
B06151	169	Thu, Sep 23, 1993 M. Lumpkin D. Scott	Information Amendment: Clinical	We have additional information on a report [redacted] dverse Event No. 081-0983-930015-00) that we submitted earlier on September 16, 1993 (Serial No. 168), as a clinical information amendment. Follow-up information obtained by Fujisawa Pharmaceutical Co. about this 64-year-old female who was hospitalized for acute renal failure 9 days after completing cefdinir for bronchitis indicates that the reporting physician now considers the event unlikely related to cefdinir. This change in causality is based on a kidney biopsy that showed changes in glomeruli, not of tubules. Tubules are susceptible to the renal toxicity of -lactam antibiotics. A revised reporting form is attached. As the [redacted] is now considered unlikely to be related to cefdinir by the reporting physicians from Japan and the Parke-Davis medical reviewer, the event will be reported as an IND safety report.
B06352	170	Wed, Sep 29, 1993 M. Lumpkin D. Scott	Protocol Amendment: New Investigator	New Investigator: 983-005-025 Protocol Filed: 10/19/92 (Ser. No. 123) Princ. Invest: [redacted] New Investigator: 983-026-029, 983-026-040, 983-026-042, 983-026-043, 983-026-044, 983-026-052 Protocol Filed: 10/21/92 (Ser. No. 125) Princ. Invest: [redacted] Princ. Invest: [redacted] Coinvestigator: [redacted] Princ. Invest: [redacted] Coinvestigator: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Coinvestigator: [redacted] Princ. Invest: [redacted]

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Barcode / Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B06352 171	Wed, Oct 06, 1993 M. Lumpkin	Information Amendment: Clinical Please refer to our fax of September 20, 1993 to Carmen Debellas of your Division, which contained a question on analysis of our sinusitis studies. We are now submitting this officially to the IND file, along with the results of a discussion we held on this issue with Drs. Ralph Harkins and Linda Sherman on September 23, 1993, at the Anti-Infective Advisory Committee Meeting. The questions were on the preferred placement for analysis of two patients who were not scheduled to receive antral punctures (taps), but who inadvertently received randomization numbers reserved for tap patients. Drs. Harkins and Sherman indicated that for the clinical evaluable patient analysis the patients should be placed with the clinical group to which they belong, i.e., the non-tap group. (Dr. Harkins said that even patients who are tapped but from whom no organism is isolated are placed in this group for analysis.) For the Intent-to-Treat meta-analysis of the sinusitis studies, the patients should be analyzed as they were randomized, i.e., in the tap group. Our analyses will follow this recommendation. If there are any further questions or comments please contact me at 313/996-1819 or FAX 313/996-7890. D. Scott
B06352 172	Mon, Oct 11, 1993 M. Lumpkin	Protocol Amendments: New Protocol New Protocol 983-049,, The Bronchoalveolar Distribution of Single-Doses of Cefdinir (CI-983) in Subjects Undergoing Diagnostic Bronchoscopy. New Protocol: 983-052,, A Single-Dose Study of Cefdinir (CI-983) Pharmacokinetics In Healthy Lactating Women and Evaluation of Cefdinir Concentrations in Breast Milk. New Protocol: 983-053 A Study of Cefdinir (CI-983) Penetration Into Sinus Tissue and Sinus Fluid in Patients Undergoing Elective Surgery on the Maxillary and Ethmoid Sinuses. D. Scott

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B06352	173	Fri, Oct 15, 1993		Pre-Meeting Briefing Package
	M. Lumpkin		Attached is a briefing package for our Cefdinir CANDA meeting on November 1, 1993, at 10:00 a.m., in Room 12B-21, at the Parklawn Building. We understand that the following persons will attend from FDA: Renata Albrecht, M.D. - Supervisory Medical Officer Carmen Debellas - Project Manager Ralph Harkins, Ph.D. - Biometrics Linda Sherman, M.D. - Medical Officer Attending from Parke-Davis will be the following: [redacted] - System Specialist, Regulatory Affairs [redacted] - Manager, Anti-Infectives, Clinical Research [redacted] - Manager, Regulatory Affairs [redacted] - System Analyst, Scientific Information Engineering Drusilla Scott, Ph.D. - Director, Regulatory Affairs [redacted] - Sr. Director, Anti-Infectives, Clinical Research [redacted] - Associate Director, Biometrics	
	D.Scott			
B06352	174	Fri, Nov 05, 1993		Protocol Amendment:s: New Investigator/Change in Protocol
	M. Lumpkin		New Investigator: 983-005-026 and 983-005-027 - Protocol Orig. Filed 10/19/92 (Ser. No. 123) Princ. Invest: [redacted] Princ. Invest: [redacted] 983-005-027 - ADDENDUM E 983-005-026 added to ADDENDUM E - Orig. Filed 9/13/93 (Ser. No. 167) New Investigator: 983-026-033 Princ. Invest: [redacted] New Invest: 983-051-012 Princ. Invest: [redacted] 983-051 - Revised pages of protocol were filed 983-051-012 - ADDENDUM A 983-036 - AMENDMENT 2 - Protocol filed 11/12/92 (Ser. No. 129) Principal Investigator addresses updated for 983-007-010, 983-006-041, 983-051-003. Several subinvestigators added to studies.	
	D. Scott			

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B06352	175	Mon, Nov 08, 1993 M. Lumpkin	Protocol Amendment: Change in Protocol Reference is made to our IND 34,738 for Cefdinir Capsules. In an early amendment (Serial No.033; Research Report No. REG 956-00111), submitted on April 18, 1991, the formulation number for 100 mg capsules in page 4 was identified as formulation 22. The correct number should be formulation 32. We have provided a replacement as Attachment 1. Please replace page 4 in the Research Report No. REG 956-00111 with the attached page. In another information amendment (Serial No. 054), submitted to you on August 21, 1991, we updated the chemistry, manufacturing and controls information to include the 300 mg capsules strength (formulation 24). For comparative clinical studies, the 300 mg capsules (size No.1) have to be encapsulated into gray/gray size No.0 capsules in order to match the encapsulated positive controls for blinding purpose. During the encapsulation operation, about 50 mg microcrystalline cellulose, NF are added to fill the empty space in the size No.0 capsules. Research Report No. RR-REG 956-00160 (Attachment 2) provides the formulation and manufacturing information for the gray/gray size 0 Cefdinir 300 mg capsules. Appendix 2 of the report presents the comparative dissolution results between the size No. 1 and encapsulated size 0 Cefdinir 300 mg capsules. The results demonstrate that an addition of about 50 mg microcrystalline cellulose has no effect on the dissolution. The specification and analytical method remain unchanged. Appendix 1 of the same report provides the stability data for the encapsulated size 0 Cefdinir 300 mg capsules. The data indicates that encapsulated capsules are stable. We will monitor the stability for the planned duration of the proposed clinical studies. We would appreciate your adding this amendment to our Cefdinir IND file. P. Chen
B06475	176	Tue, Nov 16, 1993 M. Lumpkin	Information Amendment: Clinical On November 1, 1993 we met with members of your division to discuss the upcoming NDA/CANDA for cefdinir. At that meeting, Dr. Linda Sherman, the medical reviewer, agreed to review a draft clinical report to evaluate whether some of the appendices containing clinical summary tables and data listings should be eliminated from future reports. A draft report of a urinary tract study, 983-002, is enclosed for evaluation, and a desk copy with tabs is included for Dr. Sherman. Some of the statistical appendices are not yet available, but these do not constitute the bulk of the appendices and will be available in the final report for comment. D. Scott

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/Ref#	Date / To: / From:	RE/Contents/Report No.	Report Title/ Report No.
B06492	177	Tue, Nov 23, 1993 M. Lumpkin D. Scott	New Investigator: 983-004-068 Princ. Invest: [redacted] New Investigator: 983-026-046 and 983-026-047 Princ. Invest: [redacted] Princ. Invest: [redacted]	Protocol Amendments: New Investigator
B06492	178	Wed, Nov 24, 1993 M. Lumpkin D. Scott	Reference is made to our IND 34,738 for Cefdinir Capsules and Suspension. On November 1, 1993 we held an initial meeting to discuss the functionality of the cefdinir CANDA with members of your division. Our minutes of that meeting are attached. We would appreciate any comments on them, and when available, a copy of the Agency minutes.	General Correpondence: Meeting Minutes
B06492	179	Wed, Dec 01, 1993 M. Lumpkin D. Scott	We are submitting an initial IND Safety Report on cefdinir (Adverse Event No. 081-0983-930022-00). The events being reported are peptic ulcer and eruption. They did not occur in an IND study; they were reported from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This is a case of an 11-year-old male with an upper respiratory infection who concurrently received tolmetin and cefdinir. He developed an eruption (erythema exudative multiforme) and a gastroscopy-confirmed peptic ulcer. The physician in Japan considered both events probably related to cefdinir. The Parke-Davis Medical Reviewer considered the rash possibly related to cefdinir and the peptic ulcer likely related to tolmetin rather than cefdinir. There have been no prior similar reports of peptic ulcer to our Worldwide Adverse Events Reporting System (WAERS) dababase. Erythema exudative multiforme is labelled. However, since the reporting physician considered the events probably related to cefdinir, we are submitting the information as an IND safety report.	IND Safety Report: Initial Written Report

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Product Name: Cefdinir

Barcode	Ser/Ref#	Date / To: / From:	RE/Contents/Report No.	Report Title/ Report No.
B06492	180	Thu, Dec 02, 1993 M. Lumpkin D. Scott	Please refer to Serial Nos. 168 and 169 for IND 34,738, submitted September 16 and 23, 1993 respectively. In these information amendments, we provided available data on a case of acute renal failure reported from post-marketing experience in Japan. In Serial No. 168, we noted that insufficient information was available to determine the accuracy of the diagnosis [redacted]nd the relationship to cefdinir. Shortly thereafter we obtained additional information on the basis of a [redacted] that led both the reporting Japanese physician and the Parke-Davis medical reviewer to conclude that the event was unlikely to be related to cefdinir, and reported this in Serial No. 169. Because of this lack of a reasonable association with the use of the drug, we intended to state in Serial No. 169 that the event would not be submitted as an IND safety report. The word "not" was inadvertently omitted from the relevant paragraph. The corrected paragraph is shown below, and a copy of the Serial No. 169 letter is attached for reference: "As the [redacted] is now considered unlikely to be related to cefdinir by the reporting physician from Japan and the Parke-Davis medical reviewer, the event will not be reported as an IND safety report."	Information Amendment: Clinical Correction to Previous Amendment
B06492	181	Thu, Dec 09, 1993 M. Lumpkin D. Scott	New Investigator: 983-005-029 and 983-005-030 Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-026-050 and 983-026-055 Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-037-021 and 983-037-022 Princ. Invest: [redacted] Co-Invest: [redacted]	Protocol Amendments: New Investigator
B06492	182	Tue, Dec 14, 1993 M. Lumpkin P. Chen	Attached is an information amendment to our IND 34,738, updating the stability data for the Manufacturing and Controls for Cefdinir 300 and 100 mg Capsules. Formulation No. 32 is the 100 mg capsule, whereas formulation 24 is the 300 mg capsule. In addition, we have packaged the 100 mg capsule in a blister package. The specifications for the blister package components are also provided in the attachment.	Information Amendment: Chemistry, Manufacturing and Controls
B06522	183	Tue, Dec 14, 1993 M. Lumpkin D. Scott	(2) Research Reports submitted See Research Report list for RR #, author, date and title.	Information Amendments: Clinical

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Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No.	Report Title/ Report No.
B06522	184	Fri, Jan 14, 1994 M. Lumpkin D. Scott	Information Amendment: Clinical	(1) Research Report Submitted See Research Report List for RR#, author, date and title
B06720	185	Wed, Jan 19, 1994 M. Lumpkin D. Scott	Protocol Amendments: New Investigators/Change in Protocol	New Investigator: 983-004-069, 983-004-070, 983-004-071, 983-004-072, 983-004-073 Orig. Filed 11/27/91 (Ser. No. 070) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest:: [redacted] Princ. INvest: [redacted] New Investigator: 983-006-050 Orig. Filed 5/22/92 (Ser. No. 099) Princ. Invest: [redacted] New Investigator: 983-026-051, 983-026-053, 983-026-054 Orig. Filed 10/21/92 (Ser. No. 125) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-019-006 Orig. Filed 11/24/92 (Ser. No. 131) Princ. Invest: [redacted] 983-048-000: [redacted]. replacing James A. Hedrick, M.D. as principle investigator. Added several subinvestigators Change of address for 983-004-064 [redacted]
B06720	186	Thu, Jan 27, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Investigator	New Investigator: 983-004-074 Princ. Invest: [redacted]

SubType: IND
CI#: 983 Sub Date: 4/30/90
Generic: Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B06720	187	Mon, Jan 31, 1994 M. Lumpkin	IND Safety Report: Initial Written Report In accordance with 21 CFR 312.32 (c), we are submitting an initial IND Safety Report on cefdinir (Adverse Event No. 081-0983-940016-00). The events being reported are shock and asthmatic attack. They did not occur in an IND study, rather from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This is a case of a one-year-old male with allergic bronchitis who started cefdinir when his cough became increasingly severe. On the second day of cefdinir therapy, symptoms (wheeze) progressed to status asthmaticus which was treated with a respirator. Shock was suggested by the development of dyspnea and cyanosis. Blood gases were normal. The patient was on theophylline and procaterol, as well as a mucolytic and antitussive before cefdinir was begun. A composite report from our Worldwide Adverse Events Reporting System (WAERS) database is attached, along with lists of previous reports of asthma and shock. The events were classified as serious and unexpected, and the reporting physician in Japan considered both events possibly related to cefdinir. The Parke-Davis medical reviewer considered the events a progression of the underlying disease and not likely related to cefdinir. However, since the reporting physician considered the events possibly related, we are submitting the case as an IND safety report. Also, pursuant to 21 CRF 312.32 (c), all investigators participating in cefdinir studies will be notified of these events. D. Scott
B06720	188	Tue, Feb 15, 1994 M. Lumpkin	Protocol Amendments: New Protocol/New Investigator New Protocol 983-056 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus Penicillin V in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Pediatric Patients. New Center 983-056-004. Princ. Invest: [redacted] New Investigator: 983-005-031 Princ. Invest: [redacted] D. Scott
B06720	189	Fri, Feb 25, 1994 M. Lumpkin	Protocol Amendments: New Investigator New Investigator: 983-004-075, 983-004-076, 983-004-077 New Investigator: 983-005-028 New Investigator: 983-056-001, 983-056-002, 983-056-005, 983-056-009, 983-056-011 D. Scott
B06720	190	Mon, Mar 07, 1994 M. Lumpkin	Protocol Amendment: New Investigator New Investigator: PR. 983-056-003, 983-056-006, 983-026-007 Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] D. Scott

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B06862	191	Mon, Mar 14, 1994 M. Lumpkin D. Scott	Information Amendments: Pharmacology/Toxicology/Clinical (7) Research Reports Submitted See Research Report List for RR#, author, date, title One correction submitted to RR-720-02983 IB
B06862	192	Thu, Mar 31, 1994 M. Lumpkin D. Scott	Protocol Amendments: New Investigator/Change in Protocol New Investigator: 983-005-032, 983-005-033, 983-005-034, 983-005-035 Orig. Filed 10/19/92 (Ser. No. 123) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] New Investigator: 983-056-008, 983-056-010, 983-056-012, 983-056-013, 983-056-014 Orig. Filed 2/14/94 (Ser. No. 188) Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest: [redacted] Princ. Invest. [redacted] Princ. Invest: [redacted] 983-053-000 - AMENDMENT 1 Orig. Filed 10/11/93 (Ser. No. 172) [redacted] has assumed responsibility as principal investigator, replacing [redacted]. for Protocol 983-004-053. Orig. Filed 4/10/92 (Ser. No. 094) Change of address for [redacted].D. Protocol 983-006-010 (see file) Change of IRB address for Protocol 983-004-070, 983-004-071 (see file) Added B. Ward as subinvestigator for Protocol 983-004-015 Orig. Filed 11/27/91 (Ser. No. 070). [redacted] as subinvestigators for Protocol 983-006-010 Orig. Filed 5/22/92 (Serial No. 099). [redacted] subinvestigor for Protocol 983-004-071 Orig. Filed 1/19/94 (Serial No. 185).

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
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Barcode / Ser# / Ref#	Date / To: / From:	RE / Report Title / Report No. / Contents / Report No. /
B06862	193	Fri, Apr 08, 1994 M. Lumpkin D. Scott	Request for Review of Trade Name We are requesting that the CDER Labeling and Nomenclature Committee review our proposed trade name for cefdinir, "Omnicef." Cefdinir is a broad-spectrum, semisynthetic cephalosporin for oral use. Application for the trademark Omnicef was made to the Patent and Trademark Office on August 14, 1992. Omnicef was published in the Trademark Digest on May 18, 1993, and the trademark was allowed on December 7, 1993. We would appreciate a review at the earliest possible committee meeting, which we understand will likely be in May.
B06862	194	Fri, Apr 08, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Protocol New Protocol 983-044 entitled, A Pharmacokinetic Study of Cefdinir in Patients on Chronic Haemodialysis. Princ: Invest: [redacted]CGP
B06862	195	Tue, Apr 12, 1994 M. Lumpkin D. Scott	General Correspondence: Meeting Minutes Attached are Parke-Davis' minutes of our CANDA meeting of March 9, 1994. We would appreciate any comments you have and a copy of Agency minutes if available. Desk copies are included for each FDA participant.
B06862	196	Mon, Apr 25, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Investigator New Invest: 983-005-036 Orig. filed: 10/19/92 (Serial No. 123) Principal Invest: [redacted]
B06862	197	Thu, Apr 28, 1994 M. Lumpkin D. Scott	IND Safety Report: Initial Written Report In accordance with 21 CFR 312.32 (c), we are submitting an initial IND Safety Report on cefdinir (Adverse Event No. 081-0983-940064-00). The event is ileus. It did not occur in an IND study, rather from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This unlabelled event involved or prolonged inpatient hospitalization and was considered definitely related to cefdinir, but not serious, by the reporting physician. The Parke-Davis Medical Reviewers consider the available information insufficient for assessment. However, as the report meets the FDA definition of serious, is unlabelled and was considered related to cefdinir by the reporting physician, it is being submitted as an IND safety report. There have been no prior similar reports to our Worldwide Adverse Events Reporting System (WAERS).

SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B06862	198	Wed, May 25, 1994 M. Lumpkin D. Scott	IND Safety Report: Follow-up to a Written Report Please refer to our submission of an Initial Written IND Safety Report on April 28, 1994 (Serial No. 197), in which we reported a case of ileus from post-marketing experience in Japan (Adverse Event No. 081-0983-940064-00). Ileus was reported on Day 2 of treatment with cefdinir for a post-operative wound infection. Additional information we have now obtained indicates that the patient became constipated 10 days after surgery for an incisional hernia, with the ileus developing 14 days after the surgery. The reporting physician considered the ileus secondary to severe abnormal bowel movement due to cefdinir; drug attributability has been changed from "definitely related" to "probably related" by the physician. The Parke-Davis medical reviewers consider the ileus unlikely to be related to cefdinir. A revised reporting form is attached, with the new information highlighted. The original report is also included for reference. With the receipt of this additional information, investigators have been informed of the event pursuant to 21 CFR 312.32(c).
B06862	199	Tue, Jun 14, 1994 M. Lumpkin D. Scott	Information Amendment: Clinical We are writing to inform you of a probable case of rheumatic fever in a patient in the cefdinir 5-day pediatric pharyngitis study, 983-056. Although this event is not reportable under 21 CFR 312.32(c), we felt we should notify the investigators and you regarding this occurrence. The letter sent to the investigators is attached. We will continue to review this case, and any additional significant information will be forwarded to you and the investigators. Enrollment in Study 983-056 is about 90% complete, and the study will finish as planned.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	IRE/ Report Title/ Contents/Report No./
B06862	200	Wed, Jun 15, 1994 M. Lumpkin D. Scott	IND Safety Report: Initial Written Report Please refer to our IND 34,738, for Cefdinir Capsules and Suspension. In accordance with 21 CFR 312.32 (c), we are submitting an IND Safety Report on cefdinir. This follows a 3-day telephone report made to Mr. Carmen Debellas on June 7, 1994. The events are Steven-Johnson Syndrome, Drug-Induced Hepatic Dysfunction, and Acute Respiratory Failure. They did not occur in an IND study, rather from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. This is a case of a 59-year-old woman who developed a Steven-Johnson type eruption, hepatic dysfunction and acute respiratory failure after 2 days treatment with 300 mg cefdinir for alveolar pyorrhea. She was also receiving diclofenac sodium which is labelled for similar adverse events. The referenced events were considered life threatening and definitely related to cefdinir by the reporting physician. Steven-Johnson Syndrome and Drug-Induced Hepatic Dysfunction are in Investigator's Brochure; Acute Respiratory Failure is unlabelled. A list of prior similar reports to our Worldwide Adverse Events Reporting System (WAERS) follows the reporting form.
B07038	201	Mon, Jun 20, 1994 M. Lumpkin D. Scott	General Correspondence: Meeting Materials We are submitting information in preparation for our next meeting with your Division on the cefdinir CANDA. This meeting is scheduled for June 30, 1994 at 9:00 a.m. (Room 12B-21). We have listed follow-up items from our previous meeting on March 9, 1994 that we would like to discuss. We have also included updated sample patient summaries (case report tabulations) with accompanying CRF's for three studies; uncomplicated UTI (Study 983-002), acute bronchitis (Study 983-038), and community-acquired pneumonia (Study 983-004). We understand that the following individuals will be attending from FDA: [redacted]er [redacted]roject Manager [redacted]M.D., former Medical Officer [redacted]M.S., Statistician If a new medical officer is assigned by the time of the meeting, it would be useful if he or she could also attend. [redacted] M.D. The following individuals will attend from Parke-Davis: [redacted]Sr. Systems Analyst, Research Information Systems [redacted], M.S., Sr. Clinical Scientist, Clinical Research Drusilla Scott, Ph.D., Director, Worldwide Regulatory Affairs [redacted] Sr. Director, Clinical Research [redacted]Associate Director, Biometrics

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
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Product Name: Cefdinir

Barcode Ser/Ref#	Date / To: / From:	RE/Report Title/Report No./Contents/Report No./
B07038	202 Tue, Jul 12, 1994 M. Lumpkin D. Scott	Protocol Amendment: New Protocol New Protocol 983-058 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 10-Day Regimen of Penicillin V in the Treatment of Streptococcal Pharyngitis/Tonsillitis Infections in Adult Patients. New Centers 983-058-010: Princ. Invest: [redacted] 983-058-001: Princ. Invest: [redacted] 983-058-002: Princ. Invest: [redacted], 983-058-003: Princ. Invest: Victor A. Elinoff, M.D. , 983-058-004: Princ. Invest: [redacted] M.D., 983-058-006: Princ. Invest: [redacted], and PR. 983-058-009: Princ. [redacted]
B07083	203 Thu, Jul 14, 1994 M. Lumpkin D. Scott	Information Amendments: Chemistry/Microbiology/Pharmacology/Toxicology/Clinical (10) Research Reports submitted. See Research Report List for RR#, date, author, title Resumbitted 720-02983 with revised pages i, iii, v-viii, 9 and 21
B07090	204 Fri, Jul 15, 1994 M. Lumpkin D. Scott	IND Safety Reports: Initial Written Reports In accordance with 21 CFR 312.32 (c), we are submitting two IND Safety Reports on cefdinir. These follow a 3-day telephone report made to [redacted] of your Division on July 13, 1994. Report 1 The event reported (Adverse Event No. 081-0983-940018-01), was pseudomembranous colitis, and the patient died. This did not occur in an IND study, rather it was reported from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. A 70-year-old female with a history of a cerebral embolism, heart failure, asthma, and a gastric ulcer developed a reported pseudomembranous colitis 12 days after receiving 11 days of treatment with 300 mg cefdinir daily. She died 44 days post-treatment. Follow-up information indicated that the patient died of heart failure, pneumonia, and poor nutritional state secondary to frequent diarrhea. Though pseudomemebranous colitis was ruled out by negative tests for C. difficile and C. difficile toxin, the reporting physician did not change the event term. Report 2 The events reported (Adverse Event No. 081-0983-940020-01), were gastrointestinal (GI) hemorrhage, hepatic dysfunction, and eruption (disseminated erythema). These did not occur in an IND study, rather they were reported from post-marketing experience in Japan. Initially, the report was of an 84-year-old man with a history of cerebrovascular disease and hypertension who was hospitalized for an eruption and hepatic dysfunction during treatment with cefdinir for an upper respiratory tract infection. Follow-up information indicated that the patient had died of an upper GI hemorrhage (gastroscopic proven ulcer). Hematemesis and melena appeared 4 days after steroids were begun for the eruption (8 days after cefdinir was discontinued) and death occurred 15 days after cefdinir was discontinued. The completed reporting forms for each of the patients are attached.

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Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./	Report Title/ Report No.
B07090	205	Thu, Jul 21, 1994 M. Lumpkin P. Chen	Information Amendment: Chemistry, Manufacturing and Controls	Attached is an information amendment to our IND 34,738, for Cefdinir Capsules and Suspension, updating the manufacturing processes for Cefdinir Capsules and Powder for Oral Suspension. The manufacturing processes described in earlier amendments, dated April 18, 1991 and August 21, 1991 (Serial No. 033 and 054, respectively), for capsules (100, 200 and 300 mg) have been modified slightly in the Preparation of Polyoxyl 40 Stearate/Magnesium Stearate Mixture. In step a, the polyoxyl 40 stearate solution is allowed to cool below 40 C instead of 45 C. This solution is then slowly added to the magnesium stearate in the P-K blender instead of at a rate of 300 to 500 g/min in step b. In step e, the blending time is refined to 10 minutes rather than 5-10 minutes. The process for Preparation of Capsules remains unchanged except the amount of granulation for encapsulation for each strength is described. These changes are described in the attachment. (See letter for more info.)
B07090	206	Mon, Aug 08, 1994 L. Gavrilovich D. Scott	Information Amendments: Pharmacology/Toxicology; Clinical	Submitted (1) Research Report See Research Report list for RR#, date, author, title Correction to RR-X 720-02983 submitted (orig. submitted 2/18/92, Ser. No. 087)

IND/NDA/DMF#:	34,738	IND	Doc Type: FDA CORRESPONDENCE
			SubType: IND
CI#:	983		Sub Date: 4/30/90
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Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No./ Contents/Report No./
B07090	207	Tue, Aug 09, 1994 L. Gavrilovich	Protocol Amendments: New Investigator/Change in Protocol

New Invest: 983-005 Prot. Orig. Filed 10/12/92 (Ser. No. 123)
PR. 983-005-037, Princ. Invest: [redacted]

New Invest: 983-058 Prot. Orig. Filed 7/12/94 (Ser. No. 202)
PR. 983-058-005, Princ. Invest: [redacted]
PR. 983-058-007, Princ. Invest: [redacted]
PR. 983-058-008, Princ. Invest: [redacted]

PR. 983-053-000 - AMENDMENT 2 Orig. Filed 10/11/93 (Ser. No. 172)

PR. 983-026-033 Added coinvestigators: [redacted]
[redacted] Orig. Filed 11/5/93 (Ser. No. 174)

PR. 983-026-050 - ADDENDUM D Orig. Filed 12/9/93 (Ser. No. 181)

PR. 983-044-000 - AMENDMENT 1 Orig. Filed 4/8/94 (Ser. No. 194)

PR. 983-004-061 - [redacted] has assumed responsibilities as principal investigator for this study, replacing [redacted] Orig. Filed 3/19/93 (Ser. No. 147)

PR . 983-004-040 Added subinvestigator: [redacted]
Orig. Filed 12/19/91 (Ser. No. 074)

PR. 983-004-015 Added subinvestigator: [redacted]
Orig. Filed 1/11/92 (Ser. No. 102)

PR. 983-011-032 Added subinvestigator: [redacted]
Orig. Filed 1/11/92 (Ser. No. 102)

PR. 983-006-022 Added subinvestigators: [redacted]
Orig. Filed 8/7/92 (Ser. No. 111)

PR. 983-004-064 Added subinvestigators: [redacted]
Orig. Filed 12/22/92 (Ser. No. 135)

PR. 983-004-063 Added subinvestigators: [redacted]
Orig. Filed 2/19/93 (Ser. No. 142)

PR. 983-051-008 Added subinvestigator: [redacted]
Orig. Filed 5/19/93 (Ser. No. 152)

PR. 983-053-000 Added subinvestigator: [redacted]
Orig. Filed 10/11/93 (Ser. No. 172)

PR. 983-004-072 Added subinvestigators: [redacted]

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
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Product Name: Cefdinir

Barcode	Ser/Ref#	Date / To: / From:	RE/FW: Report Title/ Report No. Contents/Report No./
			Orig. Filed: 1/19/94 (Ser. No. 185) PR. 983-056-005 Added subinvestigators: [redacted] Orig. Filed 2/25/94 (Ser. No. 189) PR. 983-056-006 Added subinvestigators: [redacted]y, [redacted] Orig. Filed 3/7/94 (Ser. No. 190) PR. 983-056-014 Added subinvestigator: [redacted] Orig. Filed 3/31/94 (Ser. No. 192) PR. 983-005-034 Added subinvestigators: [redacted] [redacted] Orig. Filed 3/31/94 (Ser. No. 192) PR. 983-056-012 Added subinvestigator: [redacted] Orig. Filed 3/31/94 (Ser. No. 192)
		D. Scott	
B07090	208	Tue, Aug 16, 1994 L. Gavrilovich	Annual Report Attached for your information and files is the Annual Report for IND 34,738, Cefdinir (CI-983) Capsules and Suspension. This report covers the period June 7, 1993 through June 6, 1994.
		D. Scott	
B07214	209	Mon, Aug 22, 1994 L. Gavrilovich	Information Amendment: Clinical (1) Research Report Submitted See Research Report List for RR #, date author, title
		D. Scott	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

C#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode/Ref#	Ser/Date/To/From	RE/Report Title/Report No./Contents/Report No./
B07222	210 Thu, Sep 15, 1994 L. Gavrilovich	General Correspondence: Briefing Package for Meeting We are submitting a briefing package for our meeting to review the clinical plan for cefdinir. The meeting is scheduled for September 22, 1994 at 10:00 a.m. We understand the following persons will attend from FDA: [redacted] - Supervisory Medical Officer, DAIDP [redacted] - Project Manager, DAIDP [redacted]D. - Supervision Statistician, Division of Biometrics [redacted] - Medical Officer, DAIDP [redacted] - Statistician, Division of Biometrics The following will attend from Parke-Davis: [redacted] - Sr. Clinical Scientist, Clinical Research Drusilla Scott, Ph.D. - Director, FDA Liaison, Worldwide Regulatory Affairs [redacted] Sr. Director, Clinical Research [redacted] - Director, Biometrics Desk copies of the packages are enclosed for each FDA attendee.
	E. Scott	
B07222	211 Thu, Sep 29, 1994 L. Gavrilovich, M.D.	General Correspondence: Meeting Minutes Minutes of meeting held with Division on September 22, 1994. We would appreciate any comments you have on the minutes, plus a copy of the Agency minutes when available. Please note that the meeting generated action items for both the Agency and Parke- Davis.
	D. Scott, Ph.D.	
B07222	212 Fri, Sep 30, 1994 L. Gavrilovich, M.D.	Protocol Amendment: New Investigator Pr. 983-058-011: Prin. [redacted] Pr. 983-058-012: Prin. Inv.: [redacted] Orig. filed July 12, 1994 (Serial No. 202)
	D. Scott	
B07222	213 Thu, Oct 13, 1994 M. Lumpkin, M.D.	Protocol Amendment: New Investigator Pr. 1003-058-013: Prin. Inv.: [redacted] Orig. filed: July 12, 1994 (Serial No. 202)
	D. Scott	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode/Ref#	Ser/To/From	Date	RE/Contents/Report No.	Report Title/Report No.
B07222	214	Fri, Oct 21, 1994	L. Gavrilovich	Information Amendment: Chemistry, Manufacturing and Control

We were informed [redacted] 34,738, for Cefdinir Capsules [redacted] The cover letter of the amendment is attached.

We, hereby, respectively request the Agency to reference this update in support of our IND. Should you have any questions regarding this submission, please contact me at 313/996-2623 or FAX 313/996-7890.

P. Chen

B07222	215	Thu, Nov 10, 1994	L. Gavrilovich	General Correspondence: Review of Trade Name

We are requesting that the CDER Labeling and Nomenclature Committee reconsider the issues discussed in its May 9, 1994 review of the proposed trade name "Omnicef" for cefdinir, and recommend approval of the name to the Division.

The attached narrative provides background and responds to the concerns raised by the Committee, with a focus on the major concern - [redacted]

D. Scott

B07222	216	Wed, Dec 07, 1994	L. Gavrilovich	Protocol Amendment: New Protocol; Information Amendment: Chemistry/Microbiology

We hereby notify you of a clinical study to be conducted in accordance with the attached Protocol 983-050-000, entitled "A Study of the Mass Balance and Metabolism of [14C]CI-983 (Cefdinir) in Healthy Male Volunteers."

Also included is Amendment 1 to the protocol which replaces the second paragraph in Section VI. A., Dosing Schedule. Drug will now be pre-weighed by Parke-Davis rather than prepared at the study site.

D. Scott

B07222	217	Mon, Dec 19, 1994	L. Gavrilovich	Protocol Amendments: New Investigators

Pr: 983-058-014: Prin. Inv.: [redacted]
Pr.: 983-058-015: Prin. Inv. [redacted]
Pr.: 983-058-016: Prin. Inv. [redacted]
Pr.: 983-058-017: Prin. Inv. [redacted]
Pr: 983-058-018: Prin. Inv. [redacted]
Pr. 983-058-019: Prin. Inv. [redacted]
Pr. 983-058-020: Prin. Inv. [redacted]
Pr. 983-058-021: Prin. Inv. [redacted]
Pr. 983-058-022: Prin. Inv. [redacted]
Pr. 983-058-023: Prin. Inv. [redacted]
Original submitted 7/12/94 (Ser. No. 202)

D. Scott

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
Cl#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	IRE/ Contents/Report No./	Report Title/ Report No.
B07222	218	Wed, Dec 21, 1994 M. Lumpkin D. Scott		Protocol Amendments: New Investigator/Change in Protocol [redacted] has assumed responsibilities as principal investigator for Study 983-004-026 replacing [redacted] Center filed on 12/12/91 (Ser. No. 073). Additional Subinvestigators: Pr. 983-004-012: New Subinvestigators: [redacted] Study Center submitted on 12/19/91 (Ser. No. 074) Pr.: 983-004-026: New Subinvestigators: [redacted] Study Center submitted on 12/12/91 (Ser. No. 073) Pr. 983-004-027: New Subinvestigators: [redacted] Study Center submitted on 4/10/92 (Ser. No. 094) Pr. 983-004-040: New Subinvestigator: [redacted] Study Center submitted on 12/19/91 (Ser. No. 074) Pr. 983-004-053: New Subinvestigators: [redacted] Study Center submitted on 3/31/94 (Ser. No. 192) Pr. 983-004-064: New Subinvestigators: [redacted] Study Center submitted on 12/22/92 (Ser. No. 135) Pr. 983-004-070: New Subinvestigators: [redacted] Study Center submitted on 1/19/94 (Ser. No. 185) Pr. 983-004-040 address change for [redacted]
B07222	219	Mon, Jan 16, 1995 L. Gavrilovich D. Scott		General Correspondence Enclosed is a background package for a meeting to be held on January 24, 1995 at 10:00 A.M. in Room 12B-45 (Parke-Davis will set up the CANDA in this room at 9:30). During the meeting, Parke-Davis will demonstrate the projected capabilities of the Cefdinir CANDA. The background package briefly describes the attributes to be demonstrated.
B07222	220	Wed, Feb 08, 1995 L. Gavrilovich P. Chen		Information Amendment: CMC Attached Research Report 956-00188 describes a proposed market-image for the 300 mg capsules. See file for description of new capsule and manufacturing and site. Attached RR 730-02289 rpovides an alternate UV method in conjunction with an IR procedure for the identificaiton of drug substance.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode / Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B07222	221 Mon, Feb 13, 1995 L. Gavrilovich D. Scott	General Correspondence Attached are the minutes of a meeting we held with the Division on the cefdinir CANDA on January 24, 1995. We appreciate the opportunity to have had this meeting. We would appreciate any comments you have on the minutes, plus a copy of any Agency minutes when available. Dr. Soreth indicated that she would provide some working definitions on significant laboratory changes form baseline; we would appreciate receiving these at her earliest convenience to plan a further discussion on safety.
B07472	222 Tue, Feb 21, 1995 L. Gavrilovich D. Scott	Information Amendments: Clinical/Chemistry/Microbiology/Pharmacology/Toxicology (14) Research Reports submitted See Research Report list for RR#, date, author, title
B07601	223 Tue, Mar 28, 1995 L. Gavrilovich D. Scott	Information Amendments: Chemistry/Microbiology/Clinical/Pharmacology/Toxicology (7) Research Reports submitted See Research Report log for authors, dates, titles and RR#
B07663	224 Mon, Apr 24, 1995 L. Gavrilovich D. Scott	Information amendments: Chemistry/Microbiology, Pharmacology/Toxicology, Clinical Attached for your information and files are nine research reports entitled:
B07665	225 Mon, May 01, 1995 C. Debellas S. Brennan	General Correspondence: Request for Pre-NDA Meeting Reference is made to IND 34,738 for Cefdinir Capsules and Suspension and to your telephone conversation of March 29, 1995 with Paul Chen of Parke-Davis requesting a pre-NDA meeting to discuss the Chemistry, Manufacturing and Controls sections of the NDAs for the respective dosage forms. We request a meeting (1.5 to to 2 hours) with [redacted] (Supervisory Chemist), [redacted] (Reviewing Chemist) and you be arranged.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B07665	226	Tue, May 16, 1995 L. Gavrilovich	Pre-Meeting Materials Reference is made to the previous correspondences between [redacted] Division and [redacted] and myself of Parke-Davis regarding a pre-NDA meeting to discuss the Chemistry, Manufacturing and Controls section of the NDAs on May 1 and 11, 1995. This letter is to confirm our pre-NDA meeting with [redacted]s on May 31, 1995 at 10:30 A.M. (Room 12B21, Parklawn). Attached are the pre-meeting materials requested. We also request an overhead slide projector in the meeting room. The proposed Parke-Davis attendees are: [redacted], Ph.D. Senior Director, Regulatory Affairs [redacted] Ph.D. Senior Manager, Regulatory Affairs [redacted], Ph.D. Director, Product Development [redacted] Ph.D. Director, Product Development [redacted] Ph.D. Senior Research Associate, Chemical Development [redacted] Ph.D. Director, Product Development
		S. Brennan	
B07665	227	Mon, May 22, 1995 L. Gavrilovich	Pre-Meeting Materials Update Reference is made to the Pre-NDA meeting Materials for Cefdinir Capsules and Suspension submitted on May 16, 1995. Due to electronic transmission errors, three figures in Section 3: Drug Product B and C were inadvertently omitted. Enclosed, please find the replacement Section 3: Drug Product B and C portion of the Pre-NDA meeting Materials.
		S. Brennan	
B07665	228	Fri, May 26, 1995 L. Gavrilovich	Information Amendment This is an information amendment to our IND 34,738, for Cefdinir Capsules and Suspension, which updates the manufacturing and controls information for capsules. Based on experiences with the equipment of our contract manufacturer, [redacted] we are revising the drying temperature range in step c. for the preparation of Polyoxyl 40 Stearate/Magnesium Stearate Mixture, but the final specification remains the same (LOD of not more than 2.5%). The change is described below: c. Dry the wet mass from step b. in a drying oven between 24 and 45 C to an LOD of not more than 2.5%. In addition, we are deleting the Loss on Drying test in the Specifications and Test Method Section for the finished product because the final granulation is manufactured by a dry blending and compaction process.
		P. Chen	

IND/NDA/DMF#:	34,738	IND	Doc Type: FDA CORRESPONDENCE
			SubType: IND
CI#:	983	Sub Date:	4/30/90
Generic:		Appr Date:	
Product Name:	Cefdinir		

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No:	Report Title/ Report No.
	229	Tue, Jun 13, 1995		Request for pre-NDA Meeting
		L. Gavrilovich	Request of a pre-NDA meeting to discuss content & format of our upcoming NDA's for Cefdinir Capsules and Oral Suspension. These NDA's will be submitted 2Q1996. This meeting will not cover NDA Items 3 and 4.	
		D. Scott		
B10108	330	Tue, Jun 20, 1995		RR 720-03489, 720-00124, 730-02289; 939-00669
		L. Gavrilovich	Cefdinir Drug Substance: IND Information Amendment for Identification By UV", by S Priebe, dated February 22, 1995 (Research Report No. 730-02289) Validation of Uniformity of Dosage Units by Weight Variation Test Method for CI-983 (Cefdinir) 300 mg Capsules", by [redacted] Research Report No. 939-00669) A Study to Evaluate the Potential Pharmacokinetic Interactions Between Maalox® and Cefdinir (CI-983) (Protocol 983-030-0)", by [redacted] 15, 1995 (Research Report 744-00124) Listings for a Phase 3, 10-Day, Investigator-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Cephalexin in the Treatment of Pediatric Patients with Uncomplicated Skin and Skin Structure Infections (Protocol 983-13)", [redacted], dated March 15, 1995 (Research Report 720-03489) A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Patients with Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-7)", by [redacted] Research Report 720-03459)	
		D. Scott		
B10195	0	Fri, Jun 30, 1995		Follow-up to Request
		M. Thomas	Enclosed are the case report forms you requested. The forms are followed by the laboratory findings, and when applicable, a site-generated change form.	
		D. Scott		
B10195	231	Fri, Jul 14, 1995		Protocol Amendment: New Protocol
		M. Fanning	We hereby notify you of a clinical study to be conducted in accordance with the attached Protocol 983-068 entitled "A Pharmacokinetic Study of Cefdinir in Patients on Chronic Hemodialysis". We are initiating this study with Center 000.	
		D. Scott		
B10195	232	Mon, Jul 17, 1995		Response to FDA Request for Information
		M. Fanning	Please refer to IND 34,738 for cefdinir capsules and suspension and to your May 28, 1991, correspondence that commented on our clinical protocols for the treatment of uncomplicated urinary tract infections and lower respiratory tract infections, which were submitted to FDA on September 24, 1990. We discussed the issues with Linda Sherman, MD, Medical Reviewer, shortly after the IND submission. When we received these comments a year later, most issues were moot. Nevertheless, we are formally responding at this time to complete and close the file on this correspondence before the NDA is submitted.	
		D. Scott		

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND

CI#: 983 | SubDate: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode / Ref#	Ser/ To: From:	Date	RE/ Report Title/ Report No/ Contents/Report No/
B10195	233	Mon, Jul 17, 1995	Response to FDA Request for Information
		M. Fanning	Please refer to IND 34,738 for cefdinir capsules and suspension, and to your May 28, 1991 correspondence that provided comments on our original IND submission of May 2, 1990.
		D. Scott	
B10209	234	Tue, Jul 18, 1995	Information Amendments: Clinical
		M. Fanning	"Listings For A Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Patients With Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-7)", by L. Bond, C. Keyserling, et al., dated June 9, 1995 (Research Report 720-03460)
		D. Scott	
B10214	235	Thu, Jul 27, 1995	RR-720-03467 and RR-720-03468
		M. Fanning	An Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Penicillin V-K in the Treatment of Pediatric Patients with Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-51), by [redacted] dated June 19, 1995 (Research Report No. 720-03467) Patient Listings for an Investigator-Blinded, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) versus Penicillin V-K in the Treatment of Pediatric Patients with Group A -Hemolytic Streptococcal Pharyngitis/Tonsillitis Infections (Protocol 983-51), by [redacted] dated June 27, 1995 (Research Report No. 720-03468)
		D. Scott	
B10251	236	Thu, Aug 03, 1995	re: Pre-NDA meeting
		M. Fanning	Attached is our background package for the pre-NDA cefdinir meeting on August 11, at 1:00 p.m., in Conference Room A of the Parklawn building. This meeting is being held to discuss the structure, format, and presentation of data for the 1996 cefdinir capsule and cefdinir suspension NDA's.
		D. Scott	
B10251	237	Wed, Aug 09, 1995	New Investigators
		M. Fanning	Regarding Protocol 983-004: Change of address for [redacted], Center 983-004-014. Numerous new subinvestigators added. Regarding Protocol 983-005: Added [redacted] as coinvestigator to 983-005-010, and [redacted] as coinvestigator to 983-005-030. Regarding Protocol 983-051: Addendum A Regarding Protocol 983-006: Addresses of [redacted] 983-006-041 and of Dr. [redacted] 983-006-020, have changed. New subinvestigators added to 010 and 018. Regarding 983-007, 983-008, 983-101, 983-100, 983-013, 983-019, 983-026, 983-037, 983-038, 983-048, 983-051, 983-056, and 983-058, new subinvestigators were added.
		D. Scott	
B10251	238	Thu, Aug 24, 1995	Protocol Amendments
		M. Fanning	Nine Research Reports: 720-03510, 720-03564, 764-02364, 764-02365, 764-02366, 764-02367, 764-02368, 764-02369 and 764-02404
		D. Scott	

IND/NDA/DMF#:	34,738	IND	Doc Type: FDA CORRESPONDENCE
			SubType: IND
CI#:	983	Sub Date:	4/30/90
Generic:		Appr Date:	
Product Name:	Cefdinir		

Barcode / Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No:
B10251	239 Tue, Aug 29, 1995	Information Amendment: CMC
	M. Fanning	This amendment describes the manufacturing and controls information for the market-image 125 and 250 mg/5 ml strawberry-flavored powder for oral suspension formulations. These market-image suspensions will be manufactured and tested physically and chemically by our contract manufacturer, [redacted] Alternatively, physical and chemical testing may be performed at our Rochester, MI facility. The microbiological testing will be performed by a contract laboratory, [redacted] Each batch of the oral suspension will be labeled and dispensed from Clinical Pharmaceutical Operations at Ann Arbor, MI. Alternatively, the labeling may be conducted at our [redacted] This information is described in Section 1.1 of the attached report.
	P. Chen	
B10473	240 Thu, Sep 14, 1995	Annual Report
	M. Fanning	Annual Report
	D. Scott	
B10473	241 Fri, Sep 29, 1995	Protocol Amendments: New Protocol
	M. Fanning	We hereby notify you of a clinical study to be conducted in accordance with the attached Protocol 983-066 entitled, A Single-Dose Bioequivalence Study Comparing 300-mg Cefdinir Capsules Used in Clinical Studies to Market-Image 300-mg Cefdinir Capsules. We are initiating this study at Parke-Davis's Community Research Clinic.
	D. Scott	
B10473	243 Wed, Oct 11, 1995	IND Safety Report: Initial Written Report
	M. Fanning	we are submitting an initial 10-Day IND Safety Report. The adverse event being reported is cholestasia. It was reported from post-marketing experience in Japan, where cefdinir is marketed by Fujisawa Pharmaceutical Company. Cholestasia was reported in a 3-year-old girl with a history of infantile CMV hepatitis who received cefdinir for 7 days for treatment of fever, coughing, and diarrhea. Liver biopsy findings were compatible with drug-induced cholestasis. [redacted]
	D. Scott	
B10473	242 Wed, Oct 11, 1995	Protocol Amendment: New Protocol
	M. Fanning	New Protocol 983-059 entitled, A Double-Blind, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 7-Day Regimen of Loracarbef in the Treatment of Acute Exacerbations of Chronic Bronchitis in Adult Patients. New Centers 983-059-003, 983-059-004, 983-059-008, and 983-059-017.
	D. Scott	
B10473	244 Tue, Oct 17, 1995	Information Amendment: Clinical
	M. Fanning	Seven Research Reports: 720-03465, 720-03466, 720-03570, 720-03571, 720-03572, 750-00268, and 764-02446 and Investigator Brochure Update, dated 6/26/95
	D. Scott	
B10473	245 Wed, Oct 25, 1995	General Correspondence: Meeting Minutes
	M. Fanning	Attached are the minutes of the cefdinir pre-NDA meeting on issues other than CMC.
	D. Scott	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. Contents/Report No./
B10844	247	Mon, Nov 13, 1995 M. Fanning P. Chen	Information Amendment: CMC Based on our manufacturing experience with both the 125 and 250 mg/5ml strengths of Cefdinir for Oral Suspension, we propose the following revisions to the specifications for these products
B10844	246	Mon, Nov 13, 1995 M. Fanning D. Scott	Protocol Amendments: New Protocol, New Investigators New Protocol 983-067 entitled, A Single-Dose Bioequivalence Study of Cefdinir Comparing 125 mg/5 ml Market-Image Suspension to the 125 mg/5 ml Suspension Used in Clinical Trials. Regarding Protocol 983-059: New Centers 983-059-001, 983-059-002, 983-059-007, 983-059-009, 983-059-010, 983-059-015, 983-059-019, 983-059-021, 983-059-023, 983-059-025.
B11391	248	Tue, Dec 05, 1995 M. Fanning D. Scott	Information Amendments: Clinical Three Research Reports: 744-00206, 720-03453 and 720-03454
B12264	249	Thu, Dec 07, 1995 M. Fanning P. Chen	Information Amendment: CMC Reference is made to our IND 34,738 for Cefdinir Capsules & Suspension & to the pre-NDA meeting on CMC issues with Drs. S. Roy, supervisory chemist, V. Shetty, reviewing chemist, and Mr. C. Debellas, CSO of your Division on 5/31/95. Attached, please find two [redacted] reports entitled, Single Dose Toxicity Study of A Related Compound of Cefdinir In Mice (Intravenous Dosing), GLR920020 and Single Intravenous Dose Toxicity Study of Related Compounds of FR80482, GLR950408 for related compounds XII, XIII & XV.
B12264	250	Mon, Dec 11, 1995 M. Fanning D. Scott	Protocol Amendments: New Protocol, New Investigators New Protocol 983-060 entitled, A Double-Blind, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 10-Day Regimen of Cefprozil in the Treatment of Acute Exacerbations of Chronic Bronchitis in Adult Patients. New Center 983-060-002. New Protocol 983-068 entitled, A Pharmacokinetic Study of Cefdinir in Patients on Chronic Hemodialysis. New Center 981-068-002. Regarding Protocol 983-059: New Centers 983-059-005, 983-059-006, 983-059-011, 983-059-012, 983-059-014, 983-059-016, 983-059-020, 983-059-021, 983-059-022 and 983-059-024.
B12264	251	Tue, Dec 12, 1995 M. Fanning D. Scott	Protocol Amendments: New Protocol New Protocol 983-065 entitled, An Open-Label Multicenter Study of a 5-Day Regimen of Cefdinir in the Treatment of Acute Suppurative Otitis Media in Pediatric Patients. New Centers 983-065-001 and 983-065-010.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CH#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode / Ref#	Ser/ To: From:	Date	RE/ Contents/Report No./	Report Title/ Report No.
B12274	252	Fri, Jan 12, 1996		Information Amendment: Clinical, Chemistry\Microbiology
	M. Fanning			Four Research Reports: 744-00145, 744-00213, 744-00214 and 720-03632
	D. Scott			
B12568	253	Mon, Jan 15, 1996		Protocol Amendment: New Investigator
	M. Fanning			Regarding Protocol 983-059: New Center 983-059-013 Regarding Protocol 983-060: New Centers 983-060-003, 983-060-004, 983-060-005, 983-060-006, 983-060-007, 983-060-008, 983-060-010, 983-060-012, 983-060-014, 983-060-015, 983-060-016, 983-060-017, 983-060-018, 983-060-019, 983-060-020 and 983-060-024 Regarding Protocol 983-065: New center 983-065-003
	D. Scott			
B12568	254	Fri, Feb 02, 1996		Information Amendments: Clinical, Pharmacology/Toxicology
	M. Fanning			Six Research Reports: 744-00221, 764-02507, 764-02498, 764-02499, 764-02500, 764-02501
	D. Scott			
B12568	255	Thu, Feb 08, 1996		Protocol Amendment: New Investigators
	M. Fanning			Regarding Protocol 983-060: New Centers 983-060-021 and 983-060-023 Regarding Protocol 983-065: New Centers 983-065-004, 983-065-007 and 983-065-009
	D. Scott			
B12568	256	Thu, Feb 08, 1996		IND Safety Report: Initial Written Report
	M. Fanning			This written report follows a telephone report I made to Mr. Carmen Debellas of your Division on 2/7/96. The adverse events being reported are acute enterocolitis and myocardial infarction. They were reported from Japanese post-marketing experience rather than clinical trials with cefdinir. The fatal myocardial infarction was considered secondary to the massive fluid shifts caused by hypoproteinemia resulting from severe colitis. The 78-year old male had received cefdinir 300 mg/day for 15 days, and died on Day 18. The reporting physician considered these events possibly related to cefdinir and to minocycline and panipenem/betamipron which the patient had received before cefdinir.
	D. Scott			
B13132	257	Wed, Feb 21, 1996		Information Amendment: Chemistry/Microbiology
	M. Fanning			This amendment provides additional toxicity information on related compounds II, III, IV, V, VII, VIII and Metabolite M-V as suggested [redacted] supervisory chemist, in the pre-NDA meeting of May 31, 1995, between representatives of Parke-Davis and your Division. Attached is Fujisawa report entitled, Acute Toxicity Study of Deterioration Product, Related Compounds and Metabolite of FR 80482 in Mice (Intravenous Dosing).
	P. Chen			

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND

CI#: 983 Sub Date: 4/30/90

Generic: Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No./ Contents/Report No./
B13132	258	Wed, Feb 21, 1996 M. Fanning D. Scott	IND Safety Report: Initial Written Report Adverse Event No. 081-0983-960007. This reports describes a 66-year-old woman who was hospitalized for vomiting and hyoptension after a single 100 mg dose of cefdinir for the treatment of acute bronchitis. Approximately 6 and one-half hours later, the blood pressure of this woman had dropped to 90/68. The patient was treated with I.B. hydrocortisone and dopamine and recovered. Though hypotension is the dominant reaction of anaphylatic shock, the term hypotension is unlabeled under the policy of reporting what has been reported and not what we think has been reported.
B13132	259	Tue, Feb 27, 1996 M. Fanning P. Chen	Information Amendment: CMC As the development of these products progresses, an improved analytical method for the impurities/degradation products for capsule and suspension products has been developed and validated. This amendment updates the method described previously in the IND for impurities/degradation products.
B13132	0	Thu, Feb 29, 1996 W. Foley D. Scott	Response to FDA Request for Information Reference is made to you 2/7/96 correspondence to [redacted] of Warner-Lambert Company. Per your request, enclosed are copies of all documents relevant to research conducted by [redacted] for Protocol 983-004 on behalf of PD.
B13293	260	Wed, Mar 06, 1996 M. Fanning D. Scott	Information Amendments: Chemistry/Microbiology and Clinical Research Report Nos. 720-03565, 720-03573, 720-03574, 720-03575, 720-03576, 720-03563, 720-03569, 720-03577, 744-00181 and 744-00212.
B13771	261	Mon, Mar 11, 1996 M. Fanning D. Scott	Information Amendments: Chemistry/Microbiology and Clinical Attached are seven research reports: 720-03562, 720-03566, 720-03567, 720-03568, 720-03578, 720-03579, and 720-03348
B13828	262	Mon, Mar 18, 1996 M. Fanning D. Scott	Information Amendments: Clinical Research Report No. 720-03456 entitled, A Phase 3, 10-Day, Double-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Cefaclor in the Treatment of Adult Patients with Community-Acquired Pheumonia (Protocol 983-4)
B14034	263	Fri, Mar 22, 1996 M. Fanning D. Scott	General Correspondence: Request for Waiver We propose to electronically submit CRFs for all patients in Phase 2/3 studies. We are also proposing to submit investigator curricula vitae electronically only. We are uncertain as to whether this requires a Center waiver or simply Divisional agreement, as the NDA regulations do not require the submission of curricula vitae in the NDA. Rather, the 1988 guidelines, "Guidelines for the Format and Content of the Clinical and Statistical Sections of a Application" request their submission.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND
CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode	Ser/Ref#	Date	RE/To:/From:	Report Title/Contents/Report No./ Report No.
B14034	264	Tue, Mar 26, 1996	M. Fanning D. Scott	Information Amendment: Clinical Correction to the Investigator's Brochure, Research Report No. 720-03510
B14034	265	Tue, Apr 02, 1996	M. Fanning D. Scott	IND Safety Report: Initial Written Report Adverse Event No. 081-0983-960012. The adverse events being reported are malaise and vomiting. They were reported from Japanese post-marketing experience rather than clinical trials with cefdinir. A 68-year old woman who received 100 mg cefdinir for lymphangitis experienced [redacted] hospitalized. The reporting physician considered the vomiting and malaise probably related to cefdinir. The Parke-Davis medical reviewer considered the events related to cefdinir. Although vomiting is listed in the Investigator's Brochure, t[redacted]
B14034	266	Tue, Apr 23, 1996	M. Fanning D. Scott	IND Safety Report: Initial Written Report Adverse Event No. 081-0983-960015. The adverse events being reported are hepatic encephalopathy and hepatic function disorder. While hepatic function disorder has been reported previously, hepatic encephalopathy has not. These events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. A 73-year old man received cefdinir 300 mg/day for 7 days for the treatment of cervical infections atheroma. Cefdinir was discontinued at this time, when enzyme elevations were noted. Forty-nine days post-treatment, he was hospitalized for hepatic encephalopathy and hepatic function disorder. The patient has not yet recovered. The reporting physician considered these events possibly related to cefdinir, but pravastatin sodium, benidipine hydrochloride, and benzbromarone were also considered suspect drugs. The Parke-Davis Medical reviewer considered the events possibly related to cefdinir.
B14034	267	Fri, Apr 26, 1996	M. Fanning P. Chen	Information Amendment: Chemistry, Manufacturing and Controls Attached is an information amendment (RR-REG 956-00217) to our IND 34,738, which updates the Chemistry, Manufacturing and Controls for cefdinir powder for oral suspension. During manufacture of the strawberry flavored suspension (Formulation 30) in accordance with the process described in the amendment of August 29, 1995 (Serial No. 239), we experienced segregation in the filling process.
B14738	268	Tue, Apr 30, 1996	M. Fanning D. Scott	Information Amendments: Clinical Two Research Reports: 720-03390 and 744-00255.
B14740	269	Thu, May 02, 1996	M. Fanning D. Scott	Information Amendment: Clinical Research Report No. 720-03463 entitled, A Phase 3, 10-Day, Investigator-Blind, Randomized, Comparative, Multicenter Study of Cefdinir (CI-983) Versus Amoxicillin/Clavulanate in the Treatment of Community-Acquired Bacterial Pneumonia (Protocol 983-26)

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B14881	270	Mon, May 06, 1996 M. Fanning D. Scott	Protocol Amendment: New Investigators New Centers 983-060-009, 981-060-011, 981-060-022, 981-060-025, 981-060-026, 981-060-027, 981-060-028, 981-060-029, 981-060-030, 981-060-031, 981-060-033 and 981-060-034. New Centers 983-065-002 and 983-065-006
B16310	271	Mon, May 06, 1996 M. Fanning D. Scott	Information Amendment: Clinical RR 720-03416
B16316	272	Thu, May 09, 1996 M. Fanning D. Scott	Information Amendment: Clinical RR 720-003378
B16682	273	Mon, May 13, 1996 M. Fanning D. Scott	Information Amendment: Clinical Research Report No. 720-03471.
B16682	274	Tue, May 21, 1996 M. Fanning D. Scott	General Correspondence: Request for Waiver - Follow-Up In our submission of 3/22/96, we requested a waiver of 21 CFR 314.50(f) for upcoming NDAs for Cefdinir Capsules and Cefdinir Suspension. This NDA requirement is for paper copies of case report forms (CFRs) for patients who died during a clinical study or who did not complete the study because of an adverse event. As a follow-up to this request, and according to FDA MAPP 6010.1, we also state that the electronic case report forms have been prepared in a manner that is substantially consistent with the FDA's proposed rules regarding electronic signatures and electronic records, proposed 21 CFR Part 11, 59 FR 45160 (8/31/94). Paper copies of the CRF's will be maintained as required under 21 CFR 312.57(b).
B17956	275	Wed, Jun 05, 1996 M. Fanning D. Scott	Information Amendment: Clinical Research Report Nos. 720-03469, 720-03717, 744-00267 and a revised Investigator's Brochure, No. 720-03510.
B19958	276	Mon, Jul 08, 1996 M. Fanning D. Scott	Protocol Amendment: Change in Protocol, New Investigators Regarding Protocol 983-067: Amendment 1 Regarding Protocol 983-026: New Center 983-026-008 Regarding Protocol 983-059: New Center 983-059-018 Regarding Protocol 983-060: New Center 983-060-032
B20334	277	Tue, Jul 09, 1996 M. Fanning D. Scott	Information Amendment: Pharmacology\Toxicology, Clinical Research Report X 764-02474, 720-03461, 744-00259 and 720-03453.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
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Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./	Report Title/ Report No.
B20335		Wed, Jul 10, 1996 D. Scott J. Woodcock	Waiver of the requirements for the submission of paper case report forms and/or case report tabulations. Waiver request granted.	
B20804	278	Wed, Jul 24, 1996 M. Fanning D. Scott	Updated Research Report No. 720-03364 entitled, A Phase 3, 10-Day, Double-Blind, Randomized, Comparative, Multicenter Study of Cedfinir (CI-983) Versus Cephalexin in the Treatment of Patients with Skin and Skin Structure Infections (Protocol 983-8).	Information Amendment: Clinical
B21248	279	Mon, Aug 19, 1996 D. Feigal, M.D. D. Scott	Adverse Event No. 081-0983-960025, an initial 10-Day safety report on cefdinir for anaphylactoid reaction (fatal). This follows a telephone call to Mr. Carmen Dellas of your Division on 8/15/96. Although ß-lactam antibiotics are prominently labeled with warnings about anaphylaxis, which always has the potential to be life-threatening or fatal, it is the policy of Parke-Davis to consider the initial death it learns of as immediately reportable. This event was not reported from PD clinical studies, rather from post-marketing experience in Japan. As reported in the attached MedWatch form, a 69-year-old man with an upper respiratory tract infection received a single 300 mg dose of cefdinir and died several hours later. He was receiving several concomitant drugs. The reporting physician considered the anaphylactoid reaction possibly related to cefdinir. The PD medical reviewer considered the event unrelated to cefdinir. Other anaphylactoid reactions previously reported to PDs' WAERS are attached. Also, all participating investigators will be notified of this event.	IND Safety Report: Initial Written Report
B21248	280	Wed, Aug 21, 1996 D. Feigal P. Chen	Amendment to Research Report Reg 730-02666.	Information Amendment: Chemistry, Manufacturing and Controls
B21248	281	Tue, Sep 17, 1996 D. Feigal D. Scott	Annual Report	Annual Report
B21248	282	Fri, Sep 20, 1996 D. Feigal D. Scott	New Protocol 983-064 entitled, An Investigator-Blinded, Randomized, Comparative, Multicenter Study of a 5-Day Regimen of Cefdinir Versus a 10-Day Regimen of Cefprozil in the Treatment of Acute Suppurative Otitis Media in Pediatric Patients. New Center 983-064-001: [redacted]	Protocol Amendment: New Protocol
B21248	283	Fri, Oct 18, 1996 D. Feigal D. Scott	Regarding Protocol 983-060: New Centers 983-060-036 and 983-060-037. Regarding Protocol 983-064: New Centers 983-064-002, 983-064-003, 983-064-006, 983-064-007, 983-064-009, 983-064-010, 983-064-011, 983-064-013, 983-064-014, and 983-064-015.	Protocol Amendments: New Investigators

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

Cl#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B21248	284	Wed, Nov 20, 1996	IND Safety Report: Initial Written Report
		D. Feigal	We are submitting an initial 10-Day safety report on cefdinir, AE 081-0983-960039. The adverse events being reported is erythema nodosum (combined with fever, fatigue, and function disorder). These events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form, a 38-year old woman who had received 7 days of cefdinir, 300 mg/day, for suppurative mastitis was hospitalized 3 days after discontinuing treatment for generalized fatigability, hepatic function disorder, fever, and erythema nodosum. She recovered from all events by Day 20.
		D. Scott	
B21248	285	Fri, Dec 06, 1996	Information Amendment: Clinical
		D. Feigal	Updated Investigator's Brochure, RR 720-03510.
		D. Scott	
B22694	286	Wed, Dec 11, 1996	Protocol Amendment: New Investigators
		D. Feigal	Regarding Protocol 983-059: New Center 983-059-024. Regarding Protocol 983-060: New Centers 983-060-006 and 983-060-035. Regarding Protocol 983-064: New Centers 983-064-005 and 983-064-008.
		D. Scott	
B22694	287	Tue, Dec 31, 1996	IND Safety Report: Initial Written Report
		D. Feigal	we are submitting an initial 10-day safety report on cefdinir (AE 081-0983-960048) for stomatitis (combined with fever and erythema). The events were not reported from PD clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form, a 48-year old woman who had received cefdinir for bronchitis developed stomatitis, erythema, and fever. She recovered, but died from breast cancer and metastatic liver cancer 11 days later. The reporting physician considered the stomatitis and erythema possibly related to cefdinir. Erythema is in the Investigator's Brochure for cefdinir; there have been no prior reports of stomatitis although there have been reports of skin disorders affecting the oral mucosa (Stevens-Johnson syndrome). The reporter did not consider the stomatitis a form of Stevens-Johnson syndrome.
		D. Scott	
B22694	288	Tue, Jan 07, 1997	Information Amendment: Clinical
		D. Feigal	On 12/31/96, we submitted an initial written report on stomatitis (Serial No. 287). Attached is the letter that was sent to all participating investigators.
		D. Scott	
B22694	289	Mon, Jan 13, 1997	Information Amendment: Clinical
		D. Feigal	The Investigator's Brochure for cefdinir (Research Report No. 720-03510)has been updated as of 1/3/97 to add the term stomatitis to the list of postmarketing adverse events. The event is also briefly described. An IND safety report on this event was submitted on 12/31/96.
		D. Scott	

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE
SubType: IND

CI#: 983 | Sub Date: 4/30/90
Generic: | Appr Date:
Product Name: Cefdinir

Barcode / Ser/ Ref#	Date To: From:	RE/ Report Title/ Report No. Contents/Report No./
B22694 290	Tue, Mar 11, 1997 D. Feigal D. Scott	Protocol Amendment: New Investigators Regarding Protocol 983-059: New Center 983-059-023 Regarding Protocol 983-060: New Centers 983-060-008 and 983-060-038.
B22694 291	Fri, Mar 14, 1997 D. Feigal P. Chen	Information Amendment: Chemistry, Manufacturing and Controls Reference is made to our IND 34,738, for Cefdinir Capsules and Suspension. This amendment (Research Report No. 939-00690) updates and summarizes the methods and specifications which were described in previous amendments (Serial Nos. 175 and 220) for the 300 mg capsules. The revised specifications are contained in Section 2.0. [redacted] [redacted]. Uniformity of dosage units (USP < 905>) is performed by weight variation since about 86% of the total fill weight is the drug substance.
B22694 292	Fri, May 09, 1997 D. Feigal D. Scott	IND Safety Report: Initial Written Report The adverse event being reported (081-0983-970016) is increased serum amylase (the labeled events of jaundice and hepatic damage were also reported). The events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form (Attachment 1), a 73-year old woman with an upper respiratory tract infection had prolonged hospitalization for jaundice, hepatic damage, and increased serum amylase 5 days after a brief treatment with cefdinir 300 mg/day. The reporting physician considered these events possibly related to cefdinir. There have been no prior reports of increased serum amylase for cefdinir. The Parke-Davis medical reviewer considered the event unlikely to be related to cefdinir because of the temporal relationship to the administration of cefdinir. All participating investigators will be notified of these events via a letter, a prototoype of which is included as Attachment 2.

IND/NDA/DMF#: 34,738 | IND | Doc Type: FDA CORRESPONDENCE | SubType: IND

CI#: 983 | Sub Date: 4/30/90

Generic: | Appr Date:

Product Name: Cefdinir

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title / Report No.
B22694	293	Thu, May 15, 1997 G. Chikami D. Scott	IND Safety Report: Initial Written Report We are submitting an initial 10-day safety report (081-0983-970019) on cefdinir. The adverse event being reported is involuntary movements (the labeled event of consciousness disturbance was also reported). The events were not reported from Parke-Davis clinical studies, rather from post-marketing experience in Japan. As reported in the MedWatch form (Attachment 1), a 6-year boy with a history of febrile convulsions experienced involuntary movements and disturbed consciousness on his first day of treatment with cefdinir 40 mg/day for pharyngitis. He was concomitantly receiving mefenamic acid. Both drugs were administered again on Day 2 and the involuntary movements recurred. Both drugs were discontinued. The reporting physician considered the involuntary movements definitely related to cefdinir. We have received no prior reports of this event. The Parke-Davis medical reviewer considered the event possibly related to cefdinir. In accordance with 21 CFR 312.32(c)(1)(i), all participating investigators will be notified of these events via a letter, a prototype of which is included as Attachment 2.
B22694	294	Fri, May 23, 1997 G. Chikami D. Scott	Updated Investigator's Brochure, Research Report No. 720-03510 The Investigator's Brochure for cefdinir has been updated as of May 9 and May 13, 1997, to add increased serum amylase and involuntary movements to the list of postmarketing adverse events. IND safety reports on these events were submitted on May 9, 1997 (Serial No. 292) and May 15, 1997 (Serial No. 293). Attached for your information and files is the latest version of the Brochure.
B22694	295	Thu, Jun 12, 1997 G. Chikami D. Scott	IND Safety Report: Second Follow-up to an Initial Written Report Attached is a MedWatch form that provides follow-up information on a previously reported adverse event (Adverse Event No. 13368). In IND Safety Reports submitted on 6/25/92 and 10/19/92 we reported on a 22-year-old male who participated in Study 983-008, a study of cefdinir in the treatment of skin and skin structure infections. In the original report, bloody diarrhea and appendicitis were reported. Based on sigmoidoscopy, the event was changed to pseudomembranous colitis in the initial follow-up report. However, the investigator has reversed his diagnosis to the originally reported bloody diarrhea based on a pathology report on a biopsy done with the sigmoidoscopy. The report indicated that changes specific for pseudomembranous colitis were not seen.
B22694	296	Wed, Aug 13, 1997 G. Chikami D. Scott	Annual Report Annual Report

EXHIBIT 11

NDA LOG

Cl#:	983	Sub Date:	
Generic:		Appr Date:	
Product Name:	Omnicef Suspension		

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B22879	1	Mon, Dec 30, 1996	Original New Drug Application
		FDA	In accordance with Section 507 of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, Parke-Davis is submitting a New Drug Application (NDA) for Omnicef™ (cefdinir) for Oral Suspension for the treatment of mild to moderate bacterial infections in an outpatient setting. The number NDA 50-749 was preassigned on November 25, 1996. As required by the Prescription Drug User Fee Act, 50% of the 1996 application fee [redacted] was sent to the Food and Drug Administration in care of Mellon Bank, Pittsburgh, Pennsylvania on December 20, 1996. A copy of the user fee transmittal letter and cover sheet are attached; our Identification Number is 2566. As stated in the December 23, 1996 publication of 1997 user fees (61 FR 67557), we understand that we will be billed for the 1997 increase since this application is being submitted by December 31, 1996. This submission includes an archival copy of the NDA (10 volumes) and review copies for each technical reviewer.
		D. Scott	
B22769		Thu, Jan 02, 1997	Desk Copy of CMC Section
		C. Collazo	Enclosed, please find a copy of CMC section (item 3) of the Omnicef™ (cefdinir) for Oral Suspension, NDA 50-749, forwarded to the FDA on December 30, 1996.
		P. Chen	
B22769		Thu, Jan 02, 1997	Desk Copy of Volume 1.1
		C. Debellas	We submitted NDA 50-749 for Omnicef™ (cefdinir) for Oral Suspension on December 30, 1996 (received by FDA on December 31, 1996). Enclosed are desk copies of Volume 1 (Index and Comprehensive Summary) for you and Ms. Duvall-Miller. The electronic version of the NDA will be loaded on January 7, 1997. Pauline Cheng will point out then, and I will note now, that Appendix 14 to Item 3.4 had to be broken into "14a" and "14b" electronically. I have noted this on the appropriate page of the index behind this cover letter.
		D. Scott	
B22769		Fri, Jan 10, 1997	Received NDA for Omnicef 12/30/96
		Drusilla Scott	We have received your NDA for Omnicef for Oral Suspension, Therapeutic Classification 3S, Date of Application, 12/30/96, Date of Receipt 12/31/96.
		James D. Bona	
B22769		Thu, Feb 20, 1997	NDA Method Validation Letter
		P. Chen	The FDA will be performing method validation studies on Omnicef 125mg/5ml for Oral Suspension, in connection with your NDA 50-749. With your cooperation we can promptly complete this portion of our evaluation of your application. In order to perform the necessary testing, the sample should consist of the following: (see file copy for list).
		N. Falcone	

SubType: NDA

CI#: 983 | Sub Date:

Generic: | Appr Date:

Product Name: Omnicef Suspension

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B22769	3	Mon, Mar 03, 1997	Minor Amendment
		D. Feigal	We are amending Item 13.3 of NDA 50-749, the debarment certification required by the Generic Drug Enforcement Act of 1992. [redacted] The amended certification follows this letter.
		D. Scott	
B22769		Fri, Mar 07, 1997	Method Validation Samples
		H. Coffman	We are sending you the following samples and documents for the method validations of our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension. (see file copy for list)
		P. Chen	
B22769		Fri, Mar 07, 1997	Method Validation Samples
		N. Falcone	We are sending you the following samples and documents for the method validations of our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension. (see file copy for list)
		P. Chen	
B22769	4	Fri, Apr 25, 1997	Response to the Draft Deficiency Letter of the Environmental Assessment Section
		D. Feigal	Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ Capsule and Powder for Oral Suspension and to the draft deficiency letter of the Environmental Assessment section (EA) of the NDAs on March 13, 1997. The combined EA for Omnicef Capsule and Powder for Oral Suspension has been separated into two individual documents for capsules and powder for oral suspension, respectively as suggested. They are included as Attachments 1 and 2. The non-confidential versions are also included as Attachments 3 and 4, respectively.
		S. Brennan	
B22769		Fri, May 09, 1997	Desk Copy
		W. Torres	Reference is made to your request to Mr. Walter Cespedes regarding Omnicef (cefdinir) Powder for Oral Suspension. As per the agreement, we are providing you with a complete copy of the Chemistry, Manufacturing and Controls portion of the Omnicef NDA. Attached, please find copies of Item 3, Volumes 1.2 through 1.5 of NDA 50-749.
		P. Chen	
B22769	5	Thu, Jul 03, 1997	Pre-Meeting Materials
		G. Chikami	Reference is made to the previous correspondences between [redacted] of your Division and myself of Parke-Davis regarding the issue of dissolution raised during the 90-day meeting on February 12, 1997.
		P. Chen	

SubType: NDA

CI#: 983 Sub Date:

Generic: Appr Date:

Product Name: Omnicef Suspension

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Report Title/ Report No. / Contents/Report No./
B22769	6	Tue, Jul 08, 1997 G. Chikami P. Chen	Name Change Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension, respectively. We were notified by our contract manufacturer [redacted] There are no changes in operations as described in the attached letter.
B22769	7	Mon, Jul 21, 1997 G. Chikami P. Chen	Meeting Minutes Reference is made to our pending NDA 50-749 for Omnicefâ (cefdinir) Powder for Oral Suspension, to the pre-meeting material (Ref. No. 5) submitted on July 3, 1997, and to teleconferences held on July 15 and 17, 1997, between representatives of Parke-Davis and [redacted]
B23612		Fri, Aug 08, 1997 Paul Chen Gary Chikami	Request for meeting minutes FDA and P/D meeting minutes for teleconferences; July 15 and 17, 1997
B23612	8	Wed, Aug 13, 1997 G. Chikami, M.D. S. Brennan	Response to theChemistry Reviewer's Draft Deficiency Letter Reference is made to our pending NDA 50-749 for Omnicefâ (cefdinir) Powder for Oral Suspension and to the draft deficiency letter of the Chemistry, Manufacturing and Controls sections of the NDA on July 21, 1997, from Dr. Srikant Pagay of your Division. For convenience of review, the comments are repeated in italics followed by our responses.
B23612	9	Wed, Aug 13, 1997 G. Chikami, M.D. P. Chen	Information Amendment: Chemistry, Manufacturing and Controls Reference is made to our pending NDA 50-749 for Omnicefâ (cefdinir) Powder for Oral Suspension and to two teleconferences on the issue of dissolution test and specification with representatives of the Office of Clinical Pharmacology and Biopharmaceutics on July 15 and 17, 1997. As committed to in the meeting, we are submitting the dissolution test procedure with the recommended specification (not less than 80 % [Q] dissolved in 30 minutes). The validation report for the dissolution procedure will be submitted before the end of September, 1997.

SubType: NDA

CI#: 983 | Sub Date:

Generic: | Appr Date:

Product Name: Omnicef Suspension

Barcode	Ser/ Ref#	Date / To: / From:	RE/ Contents/Report No./ Report Title/ Report No.
B23612	10	Wed, Aug 27, 1997	Update of Stability Data
		G. Chikami	Reference is made to our pending NDA 50-749 for Omnicefâ (cefdinir) Powder for Oral Suspension. We are updating the NDA stability data to include the 9-, 12- and 15-month time points (Appendix 12 of Volume 2 of the NDA) in Attachment 1 and a statistical analysis report (including a diskette) containing the SAS data as Attachment 2. The diskette has been scanned for all known computer viruses using McAfee V.3.0 for Windows NT. Additional stability data for the constituted suspension stored for 10 days under refrigeration (5°C) is provided as Attachment 3.
		S. Brennan	
B23612	11	Fri, Aug 29, 1997	Second Safety Update Incorporation by reference
		G. Chikami	We are submitting the second safety update to NDA 50-739 for Omnicefâ (cefdinir) capsules on August 29, 1997, (Ref. No. 28). As the update contains information on the suspension formulation of cefdinir as well as the capsule formulation, we request that the Agency incorporate the safety update into NDA 50-749 by reference.
		D. Scott	
B23612		Fri, Sep 12, 1997	Response to FDA 483
		D. Amador	Further to our conversation of 5/21/97 we have now completed the installation and qualification of the necessary change parts to allow filling of glass bottles at the [redacted]
		R. Sheroff	
B23612	12	Mon, Sep 29, 1997	Information Amendment: CMC
		G. Chikami	Reference is made to our pending NDA 50-749 for Omnicefâ (cefdinir) Powder for Oral Suspension and to the amendment submitted on August 13, 1997, for the dissolution method of the product. We are now submitting the validation report for the dissolution method. The report is provided as Attachment 1. In addition, the specification for the product and the post-approval stability protocol have been revised to include the dissolution test. The revised product specifications and post-approval stability protocol are provided as Attachments 2 and 3, respectively.
		P. Chen	
B23612		Tue, Oct 07, 1997	FDA completed review
		Drusilla Scott	FDA has completed review of the human pharmacokinetics and bioavailability section of our submissions and have the following recommendations and comments. See file copy for complete information.
		Gary Chikami	

CI#: 983 Sub Date:

Generic: Appr Date:

Product Name: Omnicef Suspension

Barcode	Ser/ Ref#	Date To: From:	RE/ Contents/Report No./ Report Title/ Report No.
B23612	13	Thu, Oct 16, 1997 G. Chikami	Final Draft Container Labels Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension, respectively. Attached, please find the final draft container labels for these two products. Attachment 1 is the label for the 300 mg Capsule. The labels for suspension product 6 oz bottle (100 mL after constitution), 4 oz bottle (60 mL after constitution), and 30 cc bottle (5 mL after constitution) are provided as Attachments 2, 3, and 4 respectively. This version has incorporated comments and recommendations from the Agency. In addition, we have revised the storage condition of the constituted suspension to include "or store refrigerated, 2-8EC (36-46EF)". The stability data supporting this statement was included in the August 27, 1997, submission (Ref. No. 10). The constitution direction for the 30 cc bottle (physician sample) has also been changed from "Add 2 teaspoon of water" to "Add 4 mL (approximately 1 teaspoonful) of water". The change in volume of water added to constitute the powder is in line with other physician samples of similar products on the market. S. Brennan
B23612	14	Mon, Oct 20, 1997 G. Chikami	Responses to Recommendations on Human Pharmacokinetics and Bioavailability Section Reference is made to our pending NDAs 50-739 and 50-749 for Omnicefâ (cefdinir) Capsules and Powder for Oral Suspension, to the teleconferences of July 15 and 17, 1997, and to the communication from you of October 7, 1997, respectively, regarding recommendations for the human pharmacokinetics and bioavailability sections of the NDAs. We agree to change the dissolution specification for the capsules from a Q value of 75% at 30 minutes to a Q value of 80% at 30 minutes. For the powder for oral suspension, the dissolution method and recommended specification were submitted on August 13, 1997 (NDA 50-749 Ref. No. 9). The method uses USP Apparatus II at 50 rpm in 900 mL pH 6.8 phosphate buffer at 37°C. The specification is a Q value of 80% at 30 minutes. The validation report for this method was submitted on September 29, 1997 (NDA 50-749 Ref. No. 12). P. Chen

SubType: NDA

CI#: 983 | Sub Date:

Generic: | Appr Date:

Product Name: Omnicef Suspension

Ser# Ref# / Barcode	RR Number: / RR Date/Sub Date		Author/ Title
1	744-00314		
B22887	12/12/96	12/30/96	A Single-Dose Bioequivalence Study of Cefdinir Compairng 125 mg/5 mL market-image suspension to the 125 mg/5 mL suspension used in clinical trials (Protocol 983-67)
10	943-00003	[redacted]	
B23612	8/25/97	8/27/97	RR-943-00003 Stability Analysis of Omnicef (Cefdinir) 125 mg/5mL POWDER FOR ORAL SUSPENSION.

SubType: NDA

CI#: 983 | Sub Date:

Generic: | Appr Date:

Product Name: Omnicef Suspension

Barcode	Date / To: / From:	RE/Contents
B22802	Wed, Jan 08, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To determine timing for the next safety update on cefdinir. An April safety update is not necessary; it can be submitted in August as planned. The project manager will try to set up a 90-day meeting for early February.
B22802	Fri, Jan 24, 1997 Joslyn Swann Kelly Tate	Ms. Swann called to inform Parke-Davis that our Cefdinir (Suspension) application fee wa Ms. Joslyn Swann called Kelly Tate to inform Parke-Davis that our Cefdinir (Suspension) application fee was deficient.
B22802	Wed, Feb 19, 1997 Dr. Matthew Thomas Drusilla L. Scott, Ph.D	To determine whether NDA 50-749 contained clinical studies. We confirmed for the Division of Scientific Investigations that Cefdinir Suspension NDA 50-749 contained no clinical efficacy studies.
B22802	Thu, Feb 27, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To notify Parke-Davis of change needed in debarment certification. [redacted]
B22802	Thu, Mar 13, 1997 Carmen Debellas Drusilla L. Scott, Ph.D	To transmit draft deficiency letter on environmental assessment. A deficiency letter on the EA was received. There do not appear to be significant scientific deficiencies.
	Wed, Mar 26, 1997 Miriam Sosa Walter Cespedes	Mr. Dan Krajewski and Mr. Walter Cespedes contacted Ms. Miriam Sosa to discuss the pr
B22802	Wed, Mar 26, 1997 Miriam Sosa Walter Cespedes	Discussed the preparedness [redacted] for the Omnicef Oral Suspension Pre-A
B22802	Fri, Apr 11, 1997 Phillip Colangelo Paul Chen	To find out how we are doing with dissolution tests and specifications. Dr. Colangelo wanted to know how we were doing on the dissolution test and in establishing a specification of the oral suspension product. I told him that we would submit the information and request a meeting when dissolution results were compiled and reviewed.
B22802	Thu, Jun 12, 1997 Beth Duvall-Miller Paul Chen	To request a meeting with Dr. Phil Colangelo on the dissolution of the product. I called Ms. Duvall-Miller and requested a meeting with Dr. Phil Colangelo on the dissolution test for our Omnicef powder for oral suspension. She stated that she would inform me of an appropriate date when she heard from Dr. Colangelo.

SubType: NDA

CI#: 983 | Sub Date:

Generic: | Appr Date:

Product Name: Omnicef Suspension

Barcode	Date / To: / From:	RE/Contents
B22802	Tue, Jun 17, 1997 Beth Duvall-Miller Paul Chen	To inform me of two possible teleconference dates for discussing the dissolution issue of Dr. Phil Colangelo is available to discuss the dissolution of Omnicef oral suspension with us on July 8 or 15, 1997.
B22802	Thu, Jul 17, 1997 Phillip Colangelo P. Chen	Dr. Phil Colangelo called and suggested that dissolution vessels with flat or convex botto Dr. Colangelo informed me that dissolution vessels of different shapes might enhance the mixing for cefdinir suspension dissolution testing. He also wanted to see the profile for the dissolution test at 15- and 18-month stations for the 3 NDA lots.
B22802	Tue, Jul 22, 1997 Beth Duvall-Miller P. Chen	To fax me the draft chemistry deficiency letter (Please see attached). The FDA faxed us a copy of the chemistry deficiency letter.
B22802	Thu, Aug 07, 1997 Beth Duvall-Miller Paul Chen	To inform us that a dissolution specification is a regulatory specification for suspensions a The Agency informs us that a dissolution specification for Cefdinir powder for oral suspension is a regulatory specification that cannot be deleted by a supplement after approval.
B22802	Mon, Aug 11, 1997 Beth Duvall-Miller Paul Chen	To inform us that Dr. S. Pagay agreed with our proposal with respect to the content and s Dr. Pagay agrees with our proposal with respect to the content and submission date for the validation report on the cefdinir suspension dissolution method.
B22802	Thu, Aug 14, 1997 Beth Duvall-Miller Paul Chen	To inform the Agency of the scope and anticipated submission date for the validation repo I informed the Agency of our validation plan and the anticipated submission date of the validation report for cefdinir suspension dissolution procedure.
B22802	Mon, Sep 22, 1997 Shrikant Pagay, Ph.D. Paul Chen	To request a diskette for the response to the deficiency letter submitted on August 13, 19 Dr. Pagay requested a diskette for our response to the chemistry deficiency letter submitted on August 13, 1997. I took the opportunity to arrange a side meeting with him on September 23, 1997 to go over some minor matters of the application.

EXHIBIT 12

ASSIGNMENT RECORDATION

TITLE SEARCH

PAT./APPL. NO.: 4,935,507

APPLICANT(S): Takao Takaya, Fumiyuki Shirai, Hitoshi Nakamura & Yasunobu Inaba

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ASSIGNOR: Takao Takaya, Fumiyuki Shirai, Hitoshi Nakamura & Yasunobu Inaba

ASSIGNEE: Fujisawa Pharmaceutical Co.

BRIEF : Assignment of Assignor's interest

EXECUTED: 07/28/88 RECORDED: 03/01/90 REEL: 5234 FRAME: 0951

Assignment Of Application

WHEREAS, I (WE) Takao Takaya, Fumiyuki Shirai, Hitoshi Nakamura and Yasunobu Inaba

of 5-87, Suimeidai 1-chome, Kawanishi-shi, HYOGO 666-01 JAPAN; 2-10, Midorigaoka 2-chome, Ikeda-shi, OSAKA 563 JAPAN; 244-1, Aogein, Mino-shi, OSAKA 562 JAPAN and 2-6-504, Kitamidorigaoka 1-chome, Toyonaka-shi, OSAKA 560 JAPAN

, respectively,

have invented certain new and useful improvements in: NOVEL CRYSTALLINE 7-[2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO]-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER)

for which an application for Letters Patent was executed on July 28, 1988, and

WHEREAS, Fujisawa Pharmaceutical Co., Ltd.

(hereinafter referred to as "ASSIGNEE") having a place of business at: 3, Doshomachi 4-chome, Higashi-ku, Osaka-shi, OSAKA 541 JAPAN

is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent that may be granted therefor in the United States and its territorial possessions and in any and all foreign countries:

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS ($5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I (WE), by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

I (WE) hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my (our) entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me (us) had this Assign ment and sale not been made.

Further, I (WE) agree that I (WE) will communicate to said ASSIGNEE or its (his) representatives any facts known to me (us) respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial posses- sions and in any and all foreign countries.

The undersigned hereby grant(s) the firm of Oblon, Fisher, Spivak, McClelland & Maier, P.C. of 1755 S. Jefferson Davis Highway, Crystal Square, Arlington, Virginia 22202 the power to insert on this assignment any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

EXECUTED AT: Osaka, Japan

Date: July 28, 1988 — Takao Takaya (Signature of Inventor) Takao Takaya

Date: July 28, 1988 — Fumiyuki Shirai (Signature of Inventor) Fumiyuki Shirai

Date: July 28, 1988 — Hitoshi Nakamura (Signature of Inventor) Hitoshi Nakamura

Date: July 28, 1988 — Yasunobu Inaba (Signature of Inventor) Yasunobu Inaba

Date: _____ (Signature of Inventor)

Date: _____ (Signature of Inventor)

Date: _____ (Signature of Inventor)

Date: _____ (Signature of Inventor)

OBLON, FISHER, SPIVAK, McCLELLAND & MAIER, P.C.
PATENT & TRADEMARK ATTORNEYS
CRYSTAL SQUARE FIVE - SUITE 400
1755 S. JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent No. 4,935,507
Issued	:	June 19, 1990
Patentees	:	Takao Takaya Fumiyuki Shirai Hitoshi Nakamura Yasunobu Inaba
For	:	CRYSTALLINE 7-[2-(2-AMINOTHIAZOL-4-YL)-2-HYDROXYIMINOACETAMIDO]-3-VINYL-3-CEPHEM-4-CARBOXYLIC ACID (SYN ISOMER)

Box Patent Ext.
Assistant Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF AN APPLICATION

FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (an original and a certified duplicate original with declaration and attachments thereto) of the above-captioned patent for the Product Omnicef® (cefdinir suspension), the NDA for which was approved on December 4, 1997.

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-carried to the U.S. Patent and Trademark Office.

CAD01238.040

[X] A prescribed fee in the amount of $ 1,120.00 is required for the application presented.
Please charge Deposit Account No. 23-0455 in the amount of the prescribed fee above, or such greater or lesser amount as the Commissioner determines is required by law. This letter is submitted in triplicate for deposit account purposes.

Respectfully submitted,

January 26, 1998
Date

Charles W. Ashbrook
Registration No. 27,610
Assistant General Counsel,
Pharmaceutical Patents
WARNER-LAMBERT COMPANY
Parke-Davis Pharmaceutical
Research Division
2800 Plymouth Road
Ann Arbor, Michigan 48105
Tel: (313) 996-5215
Fax: (313) 996-1553

Attachments:

[X] An original APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156 with Declaration and attachments thereto.

[X] A certified DUPLICATE APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] Three (3) working copies of APPLICATION FOR EXTENSION OF PATENT TERM with Declaration and attachments thereto.

[X] This Transmittal Form in triplicate for deposit account purposes.

[X] Return Post Card.

CAD01238.040